Clinical trial results:
Efficacy and Safety of a Novel Tetravalent Dengue Vaccine in Healthy Children Aged 2 to 14 Years in Asia

Summary

EudraCT number	2014-001708-24
Trial protocol	Outside EU/EEA
Global end of trial date	

Results information

Result version number	v1
This version publication date	08 February 2016
First version publication date	17 April 2015

Trial information

Trial identification

Sponsor protocol code	CYD14

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01373281
WHO universal trial number (UTN)	U1111-1116-4957

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	2, avenue Pont Pasteur, Lyon Cedex 07, France, F-69367
Public contact	Director, Clinical Development, Sanofi Pasteur SA, +65 6431 2359, Anh.Wartel-Tram@sanofipasteur.com
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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	Interim
Date of interim/final analysis	28 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

Efficacy of CYD dengue vaccine after 3 vaccinations at 0, 6 and 12 months in preventing symptomatic virologically-confirmed dengue cases, regardless of the severity, due to any of the four serotypes in children aged 2 to 14 years at the time of inclusion.

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 were 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	03 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Philippines: 3501
Country: Number of subjects enrolled	Malaysia: 1401
Country: Number of subjects enrolled	Vietnam: 2333
Country: Number of subjects enrolled	Thailand: 1170
Country: Number of subjects enrolled	Indonesia: 1870
Worldwide total number of subjects	10275
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)	7946
Adolescents (12-17 years)	2329
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 03 June 2011 to 01 December 2011 at 9 sites in Indonesia, 5 in Malaysia, 3 in Thailand, 5 in Philippines, and 2 in Vietnam.

Pre-assignment

Screening details:

A total of 10275 subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled; 3 subjects were not vaccinated and were excluded from the Full Analysis Set for Efficacy and the Safety Analysis Set.

Period 1

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

Blinding implementation details:

An observer-blind procedure was followed for the 3 CYD dengue vaccine or placebo injections. The 'vaccinator' in charge of preparing and administering the vaccines was not authorized to collect safety data and also ensured that the documents on randomization were stored in a secure place with no unathorized access.

Arms

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

Arm description:

Subjects received 3 doses of CYD dengue vaccine; one each at 0, 6, and 12 months.

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

Dosage and administration details:

0.5 mL, subcutaneous, 3 doses at 0, 6, and 12 months.

Arm title	Placebo Group

Arm description:

Subjects received 3 doses of placebo vaccine, one each at 0, 6, and 12 months.

Arm type	Placebo
Investigational medicinal product name	Placebo (NaCl)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous, 3 doses at 0, 6, and 12 months.

Number of subjects in period 1	CYD Dengue Vaccine Group	Placebo Group
Started	6851	3424
Completed	6772	3379
Not completed	79	45
Consent withdrawn by subject	52	31
Adverse event, non-fatal	4	4
Serious adverse event	6	5
Lost to follow-up	4	1
Protocol deviation	13	4

Baseline characteristics

Reporting groups	
Reporting group title	CYD Dengue Vaccine Group
Reporting group description:	
Subjects received 3 doses of CYD dengue vaccine; one each at 0, 6, and 12 months.	
Reporting group title	Placebo Group
Reporting group description:	
Subjects received 3 doses of placebo vaccine, one each at 0, 6, and 12 months.	

Reporting group values	CYD Dengue Vaccine Group	Placebo Group	Total
Number of subjects	6851	3424	10275
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)	5296	2650	7946
Adolescents (12-17 years)	1555	774	2329
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	8.8	8.8	
standard deviation	± 3.45	± 3.42	-
Gender categorical Units: Subjects			
Female	3524	1767	5291
Male	3327	1657	4984

End points

End points reporting groups

Reporting group title	CYD Dengue Vaccine Group
Reporting group description:	
Subjects received 3 doses of CYD dengue vaccine; one each at 0, 6, and 12 months.	
Reporting group title	Placebo Group
Reporting group description:	
Subjects received 3 doses of placebo vaccine, one each at 0, 6, and 12 months.	

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

End point title	Vaccine Efficacy Against Symptomatic Virologically-confirmed Dengue Cases Due to Any Serotype 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 (temperature ≥38°C on at least 2 consecutive days) and confirmed by dengue reverse transcriptase-polymerase chain reaction and/or dengue NS1 enzyme-linked immunosorbent assay.
Cases defined as number of subjects with at least one symptomatic VCD episode from 28 days post-injection 3 to the end of Active Phase.
Density incidence: data are cases per 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. Data presented is the sum of individual units of time for which the participants contributed to the analyses.
Incidence density was calculated as the number of VCD cases divided by the cumulative person-years at risk. The vaccine efficacy is considered as significant if the lower bound of its 95% CI (exact method by Breslow & Day) is greater than 25%.

End point type	Primary

End point timeframe:

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

End point values	CYD Dengue Vaccine Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6710	3350		
Units: Cases				
number (not applicable)				
Symptomatic virologicaly-confirmed dengue cases	117	133		
Person-years at risk	6526	3227		
Density incidence	1.8	4.1		

Statistical analyses

Statistical analysis title	Vaccine efficacy of the 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. The vaccine efficacy of the CYD dengue vaccine was considered significant if the lower bound of its 95% CI was greater than 25%.

Comparison groups	CYD Dengue Vaccine Group v Placebo Group
Number of subjects included in analysis	10060
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Vaccine efficacy (%)
Point estimate	56.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	43.8
upper limit	66.4

Secondary: Geometric Mean Titers of Antibodies Against Each Serotype with the Parental Dengue Virus Strain Before and Following Injection with CYD Dengue Tetravalent Vaccine

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

End point description:

Geometric mean titers against each serotypes of the Dengue virus strains were assessed using the plaque reduction neutralization test (PRNT) in a predefined subset of 2,000 subjects from each country (1,333 in the CYD Dengue Vaccine Group and 667 in the Control Group).

End point type	Secondary

End point timeframe:

Pre-Injection 1 (Day 0) and Post-Injection 2 (6 months), and 3 (12 months)

End point values	CYD Dengue Vaccine Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1323	660		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Dengue virus Serotype 1; Pre-Injection 1	38.3 (33.8 to 43.5)	42.1 (35 to 50.6)		
Dengue virus Serotype 1; Post-Injection 2	153 (137 to 170)	46.1 (38.2 to 55.7)		
Dengue virus Serotype 1; Post-Injection 3	166 (150 to 183)	46.6 (38.7 to 56.1)		
Dengue virus Serotype 1; Year 1 post-injection 3	105 (92.8 to 119)	57.3 (46.9 to 70)		
Dengue virus Serotype 2; Pre-Injection 1	55.3 (48.7 to 62.9)	62.1 (51.7 to 74.7)		
Dengue virus Serotype 2; Post-Injection 2	360 (329 to 394)	69.5 (57.7 to 83.6)		

Dengue virus Serotype 2; Post-Injection 3	355 (327 to 386)	68.5 (57.1 to 82.2)		
Dengue virus Serotype 2; Year 1 post-injection 3	194 (175 to 214)	78.4 (65.1 to 94.4)		
Dengue virus Serotype 3; Pre-Injection 1	40.1 (35.6 to 45.1)	40.7 (34.5 to 48)		
Dengue virus Serotype 3; Post-Injection 2	203 (184 to 223)	40.8 (34.6 to 48.1)		
Dengue virus Serotype 3; Post-Injection 3	207 (189 to 226)	42.5 (36.2 to 49.9)		
Dengue virus Serotype 3; Year 1 post-injection 3	186 (168 to 206)	62.4 (51.9 to 74.9)		
Dengue virus Serotype 4; Pre-Injection 1	25.3 (22.9 to 28)	26.2 (22.6 to 30.3)		
Dengue virus Serotype 4; Post-Injection 2	151 (139 to 163)	24.4 (21.3 to 28.1)		
Dengue virus Serotype 4; Post-Injection 3	151 (141 to 162)	26 (22.6 to 29.8)		
Dengue virus Serotype 4; Year 1 post-injection 3	85.5 (78.5 to 93)	26.2 (22.5 to 30.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Antibody Titer ≥ 10 (1/dil) Against Each Serotype with the Parental Dengue Virus Strains Before and Post-injection with CYD Dengue Tetravalent Vaccine

End point title	Percentage of Subjects with Antibody Titer ≥ 10 (1/dil) Against Each Serotype with the Parental Dengue Virus Strains Before and Post-injection with CYD Dengue Tetravalent Vaccine

End point description:

Antibody titers against each serotype of the Dengue virus strains were assessed using the plaque reduction neutralization test (PRNT).

End point type	Secondary

End point timeframe:

Pre-Injection 1 (Day 0) and Post-Injection 2 (6 months) and 3 (12 months)

End point values	CYD Dengue Vaccine Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1323	660		
Units: Percentage of subjects				
number (not applicable)				
Dengue virus Serotype 1; Pre-Injection 1	52	51.3		
Dengue virus Serotype 1; Post-Injection 2	88.9	54.4		
Dengue virus Serotype 1; Post-Injection 3	94	55.4		
Dengue virus Serotype 1; 1-Year post-injection 3	79.8	55.7		

Dengue virus Serotype 2; Pre-Injection 1	58	59.3		
Dengue virus Serotype 2; Post-Injection 2	97.3	62.4		
Dengue virus Serotype 2; Post-Injection 3	98.7	61.8		
Dengue virus Serotype 2; 1-Year post-injection 3	92	65.8		
Dengue virus Serotype 3; Pre-Injection 1	56.8	59.4		
Dengue virus Serotype 3; Post-Injection 2	95.7	60.2		
Dengue virus Serotype 3; Post-Injection 3	97	61		
Dengue virus Serotype 3; 1-Year post-injection 3	93.6	62.6		
Dengue virus Serotype 4; Pre-Injection 1	51.6	50.7		
Dengue virus Serotype 4; Post-Injection 2	95.1	51.8		
Dengue virus Serotype 4; Post-Injection 3	97	53.9		
Dengue virus Serotype 4; 1-Year post-injection 3	89.4	50.7		

Statistical analyses

No statistical analyses for this end point

Secondary: 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 (2-11 years): Pain, Incapacitating, unable to perform usual activities; Erythema and Swelling, ≥50 mm. Grade 3 Solicited injection site reactions (12-14 years): Pain, Significant, prevents daily activity; Erythema and Swelling, >100 mm. Grade 3 Solicited injection site reactions: Fever, ≥39°C; Headache, Malaise, Myalgia, and Asthenia, Significant, prevents daily activity.

End point type	Secondary

End point timeframe:

Day 0 (post-vaccination) up to 14 days post-any vaccination

End point values	CYD Dengue Vaccine Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1334	663		
Units: Percentage of subjects				
number (not applicable)				
Inj. site Pain; Post-Any Inj.	46.1	41.5		
Grade 3 Inj. site Pain; Post-Any Inj.	0.1	0		

Inj. site Erythema; Post-Any Inj.	8	7.8		
Grade 3 Inj. site Erythema; Post-Any Inj.	0	0.2		
Inj. site Swelling; Post-Any Inj.	5.1	5		
Grade 3 Inj. site Swelling; Post-Any Inj.	0	0		
Inj. site Pain; Post-Inj. 1	30.5	29.6		
Grade 3 Inj. site Pain; Post-Inj. 1	0.1	0		
Inj. site Erythema; Post-Inj. 1	4.7	5.3		
Grade 3 Inj. site Erythema; Post-Inj. 1	0	0		
Inj. site Swelling; Post-Inj. 1	3	2.9		
Grade 3 Inj. site Swelling; Post-Inj. 1	0	0		
Inj. site Pain; Post-Inj. 2	23	20.5		
Grade 3 Inj. site Pain; Post-Inj. 2	0	0		
Inj. site Erythema; Post-Inj. 2	3.3	3		
Grade 3 Inj. site Erythema; Post-Inj. 2	0	0		
Inj. site Swelling; Post-Inj. 2	1.9	1.1		
Grade 3 Inj. site Swelling; Post-Inj. 2	0	0		
Inj. site Pain; Post-Inj. 3	21.6	18		
Grade 3 Inj. site Pain; Post-Inj. 3	0	0		
Inj. site Erythema; Post-Inj. 3	2.7	2.4		
Grade 3 Inj. site Erythema; Post-Inj. 3	0	0.2		
Inj. site Swelling; Post-Inj. 3	1.4	1.5		
Grade 3 Inj. site Swelling; Post-Inj. 3	0	0		
Fever; Post-Any Inj.	18.6	17.8		
Grade 3 Fever; Post-Any Inj.	3.8	2.7		
Headache; Post-Any Inj.	42.2	39.1		
Grade 3 Headache; Post-Any Inj.	1.7	1.4		
Malaise; Post-Any Inj.	35.7	36		
Grade 3 Malaise; Post-Any Inj.	1.4	1.4		
Myalgia; Post-Any Inj.	31.1	29.7		
Grade 3 Myalgia; Post-Any Inj.	0.6	0.3		
Asthenia; Post-Any Inj.	28.4	25.2		
Grade 3 Asthenia; Post-Any Inj.	1.1	2		
Fever; Post-Inj. 1	7.7	6.8		
Grade 3 Fever; Post-Inj. 1	1.4	1.1		
Headache; Post-Inj. 1	29.1	25.3		
Grade 3 Headache; Post-Inj. 1	0.5	0.9		
Malaise; Post-Inj. 1	23.4	22.3		
Grade 3 Malaise; Post-Inj. 1	0.5	0.6		
Myalgia; Post-Inj. 1	19.1	18.7		
Grade 3 Myalgia; Post-Inj. 1	0.2	0.3		
Asthenia; Post-Inj. 1	17.2	14.6		
Grade 3 Asthenia; Post-Inj. 1	0.4	0.8		
Fever; Post-Inj. 2	6.8	6.7		
Grade 3 Fever; Post-Inj. 2	1.4	1.4		
Headache; Post-Inj. 2	18.7	17.9		
Grade 3 Headache; Post-Inj. 2	0.9	0.5		
Malaise; Post-Inj. 2	14.6	15.2		
Grade 3 Malaise; Post-Inj. 2	0.5	0.6		
Myalgia; Post-Inj. 2	13.2	14		
Grade 3 Myalgia; Post-Inj. 2	0.2	0		
Asthenia; Post-Inj. 2	12	11.2		

Grade 3 Asthenia; Post-Inj. 2	0.4	0.9		
Fever; Post-Inj. 3	5.8	6		
Grade 3 Fever; Post-Inj. 3	1.2	0.3		
Headache; Post-Inj. 3	16.7	17.3		
Grade 3 Headache; Post-Inj. 3	0.5	0.2		
Malaise; Post-Inj. 3	13.9	15.9		
Grade 3 Malaise; Post-Inj. 3	0.5	0.2		
Myalgia; Post-Inj. 3	11.9	11.6		
Grade 3 Myalgia; Post-Inj. 3	0.2	0		
Asthenia; Post-Inj. 3	10.8	11.2		
Grade 3 Asthenia; Post-Inj. 3	0.3	0.3		

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-third vaccination.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	CYD Dengue Vaccine Group

Reporting group description:

Subjects who received 3 doses of CYD dengue vaccine at 0, 6, and 12 months.

Reporting group title	Placebo Group

Reporting group description:

Subjects who received 3 doses of placebo at 0, 6, and 12 months.

Serious adverse events	CYD Dengue Vaccine Group	Placebo Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	355 / 6848 (5.18%)	220 / 3424 (6.43%)	
number of deaths (all causes)	4	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip neoplasm benign			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipoma			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin papilloma			

subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Postpartum haemorrhage			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
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			
Hernia obstructive			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (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	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	2 / 6848 (0.03%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			

subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food allergy			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Child abuse			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Physical assault			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Victim of sexual abuse			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian haemorrhage			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	8 / 6848 (0.12%)	5 / 3424 (0.15%)	
occurrences causally related to treatment / all	0 / 12	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial hyperreactivity			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychosomatic disease			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
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			
Animal bite			
subjects affected / exposed	1 / 6848 (0.01%)	2 / 3424 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropod bite			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (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 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			

subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	7 / 6848 (0.10%)	2 / 3424 (0.06%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear injury			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye injury			
subjects affected / exposed	1 / 6848 (0.01%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	6 / 6848 (0.09%)	3 / 3424 (0.09%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body			

subjects affected / exposed	2 / 6848 (0.03%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body in eye			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital injury			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (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	2 / 6848 (0.03%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	2 / 6848 (0.03%)	3 / 3424 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Humerus fracture			
subjects affected / exposed	5 / 6848 (0.07%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 6848 (0.01%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			

subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Near drowning			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Open wound			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (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	3 / 6848 (0.04%)	2 / 3424 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	19 / 6848 (0.28%)	3 / 3424 (0.09%)	
occurrences causally related to treatment / all	0 / 19	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Scrotal haematoma			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Snake bite			
subjects affected / exposed	3 / 6848 (0.04%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	2 / 6848 (0.03%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 6848 (0.01%)	2 / 3424 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal injury			

subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	2 / 6848 (0.03%)	2 / 3424 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatic heart disease			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (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			
Acute disseminated encephalomyelitis			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complex partial seizures			

subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	2 / 6848 (0.03%)	2 / 3424 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	3 / 6848 (0.04%)	3 / 3424 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile convulsion			
subjects affected / exposed	11 / 6848 (0.16%)	5 / 3424 (0.15%)	
occurrences causally related to treatment / all	0 / 18	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 6848 (0.01%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			
subjects affected / exposed	2 / 6848 (0.03%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Choroidal dystrophy			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal oedema			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 6848 (0.07%)	2 / 3424 (0.06%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	3 / 6848 (0.04%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			

subjects affected / exposed	4 / 6848 (0.06%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	2 / 6848 (0.03%)	2 / 3424 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	12 / 6848 (0.18%)	2 / 3424 (0.06%)	
occurrences causally related to treatment / all	0 / 12	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	3 / 6848 (0.04%)	2 / 3424 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland mucocoele			

subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (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	1 / 6848 (0.01%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Henoch-Schonlein purpura			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 6848 (0.01%)	2 / 3424 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Glomerulonephritis acute			
subjects affected / exposed	2 / 6848 (0.03%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post streptococcal glomerulonephritis			
subjects affected / exposed	4 / 6848 (0.06%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (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			
Exostosis			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fasciitis			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture malunion			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (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	2 / 6848 (0.03%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess of external auditory meatus			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (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 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute tonsillitis			
subjects affected / exposed	2 / 6848 (0.03%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoiditis			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amoebiasis			
subjects affected / exposed	3 / 6848 (0.04%)	3 / 3424 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amoebic dysentery			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	9 / 6848 (0.13%)	7 / 3424 (0.20%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	2 / 6848 (0.03%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 6848 (0.01%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	8 / 6848 (0.12%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	4 / 6848 (0.06%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brucellosis			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (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	2 / 6848 (0.03%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis infective			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (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	50 / 6848 (0.73%)	64 / 3424 (1.87%)	
occurrences causally related to treatment / all	0 / 50	0 / 64	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	1 / 6848 (0.01%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis viral			

subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	2 / 6848 (0.03%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	26 / 6848 (0.38%)	22 / 3424 (0.64%)	
occurrences causally related to treatment / all	0 / 28	0 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis bacterial			
subjects affected / exposed	1 / 6848 (0.01%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 6848 (0.01%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	2 / 6848 (0.03%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand-foot-and-mouth disease			
subjects affected / exposed	2 / 6848 (0.03%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis A			

subjects affected / exposed	1 / 6848 (0.01%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpangina			
subjects affected / exposed	1 / 6848 (0.01%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hordeolum			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	3 / 6848 (0.04%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis bacterial			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaria			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Measles			
subjects affected / exposed	2 / 6848 (0.03%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			

subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	10 / 6848 (0.15%)	6 / 3424 (0.18%)	
occurrences causally related to treatment / all	0 / 10	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	10 / 6848 (0.15%)	2 / 3424 (0.06%)	
occurrences causally related to treatment / all	0 / 10	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasmodium falciparum infection			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	10 / 6848 (0.15%)	5 / 3424 (0.15%)	
occurrences causally related to treatment / all	0 / 10	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia primary atypical			
subjects affected / exposed	2 / 6848 (0.03%)	2 / 3424 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	3 / 6848 (0.04%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	2 / 6848 (0.03%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	3 / 6848 (0.04%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			

subjects affected / exposed	3 / 6848 (0.04%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis bacterial			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Typhoid fever			
subjects affected / exposed	5 / 6848 (0.07%)	5 / 3424 (0.15%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	4 / 6848 (0.06%)	3 / 3424 (0.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	12 / 6848 (0.18%)	7 / 3424 (0.20%)	
occurrences causally related to treatment / all	0 / 12	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
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	11 / 6848 (0.16%)	9 / 3424 (0.26%)	
occurrences causally related to treatment / all	0 / 11	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral rash			

subjects affected / exposed	0 / 6848 (0.00%)	2 / 3424 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 6848 (0.03%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	0 / 6848 (0.00%)	1 / 3424 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	2 / 6848 (0.03%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 6848 (0.01%)	0 / 3424 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	CYD Dengue Vaccine Group	Placebo Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	614 / 6848 (8.97%)	275 / 3424 (8.03%)	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed[1]	562 / 1332 (42.19%)	259 / 663 (39.06%)	
occurrences (all)	853	399	
General disorders and administration site conditions			
Injection site pain			
alternative assessment type: Systematic			

subjects affected / exposed[2]	614 / 1332 (46.10%)	275 / 663 (41.48%)	
occurrences (all)	992	449	
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed[3]	107 / 1332 (8.03%)	52 / 663 (7.84%)	
occurrences (all)	142	71	
Injection site swelling			
alternative assessment type: Systematic			
subjects affected / exposed[4]	68 / 1332 (5.11%)	33 / 663 (4.98%)	
occurrences (all)	84	36	
Fever			
alternative assessment type: Systematic			
subjects affected / exposed[5]	248 / 1332 (18.62%)	118 / 663 (17.80%)	
occurrences (all)	269	128	
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed[6]	476 / 1332 (35.74%)	239 / 663 (36.05%)	
occurrences (all)	687	352	
Asthenia			
alternative assessment type: Systematic			
subjects affected / exposed[7]	378 / 1332 (28.38%)	167 / 663 (25.19%)	
occurrences (all)	529	244	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed[8]	63 / 1334 (4.72%)	48 / 663 (7.24%)	
occurrences (all)	69	61	
Rhinorrhoea			
subjects affected / exposed[9]	46 / 1334 (3.45%)	36 / 663 (5.43%)	
occurrences (all)	48	43	
Musculoskeletal and connective tissue disorders			
Myalgia			
alternative assessment type: Systematic			

subjects affected / exposed[10]	414 / 1332 (31.08%)	197 / 663 (29.71%)	
occurrences (all)	585	292	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed[11]	85 / 1334 (6.37%)	45 / 663 (6.79%)	
occurrences (all)	113	61	
Upper respiratory tract infection			
subjects affected / exposed[12]	95 / 1334 (7.12%)	54 / 663 (8.14%)	
occurrences (all)	104	62	

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: As predefined in the protocol, reactogenicity and immunogenicity were evaluated in a subset of 2,000 subjects from each country (1,333 in the CYD Dengue Vaccine Group and 667 in the Control Group).

[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: As predefined in the protocol, reactogenicity and immunogenicity were evaluated in a subset of 2,000 subjects from each country (1,333 in the CYD Dengue Vaccine Group and 667 in the Control Group).

[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: As predefined in the protocol, reactogenicity and immunogenicity were evaluated in a subset of 2,000 subjects from each country (1,333 in the CYD Dengue Vaccine Group and 667 in the Control Group).

[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: As predefined in the protocol, reactogenicity and immunogenicity were evaluated in a subset of 2,000 subjects from each country (1,333 in the CYD Dengue Vaccine Group and 667 in the Control Group).

[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: As predefined in the protocol, reactogenicity and immunogenicity were evaluated in a subset of 2,000 subjects from each country (1,333 in the CYD Dengue Vaccine Group and 667 in the Control Group).

[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: As predefined in the protocol, reactogenicity and immunogenicity were evaluated in a subset of 2,000 subjects from each country (1,333 in the CYD Dengue Vaccine Group and 667 in the Control Group).

[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: As predefined in the protocol, reactogenicity and immunogenicity were evaluated in a subset of 2,000 subjects from each country (1,333 in the CYD Dengue Vaccine Group and 667 in the Control Group).

[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: As predefined in the protocol, reactogenicity and immunogenicity were evaluated in a subset of 2,000 subjects from each country (1,333 in the CYD Dengue Vaccine Group and 667 in the Control Group).

[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: As predefined in the protocol, reactogenicity and immunogenicity were evaluated in a subset of 2,000 subjects from each country (1,333 in the CYD Dengue Vaccine Group and 667 in the Control Group).

[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: As predefined in the protocol, reactogenicity and immunogenicity were evaluated in a

subset of 2,000 subjects from each country (1,333 in the CYD Dengue Vaccine Group and 667 in the Control Group).
[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: As predefined in the protocol, reactogenicity and immunogenicity were evaluated in a subset of 2,000 subjects from each country (1,333 in the CYD Dengue Vaccine Group and 667 in the Control Group).
[12] - 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: As predefined in the protocol, reactogenicity and immunogenicity were evaluated in a subset of 2,000 subjects from each country (1,333 in the CYD Dengue Vaccine Group and 667 in the Control Group).

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2011	The 'Other Objectives' section was revised to improve specificity of confirmation of dengue in line with the non-primary endpoint suggested in the WHO guidelines (version 2.0); It was also specified that the safety surveillance will be conducted by the Principal Investigators.
03 August 2011	Clarified the issue of sample collection times and the reporting period; Extended the collection of all SAEs to the entire study period; Noted that laboratory staff is blinded to treatment allocation and also the stratification by age as (2 to 5 years, 6 to 11 years, and 12 to 14 years); and updated the time window for assessment of serious viscerotropic disease in-line with the update of the Guidelines for Assessing Viscerotropic and Neurotropic Adverse Events, and introduced the use of the WHO Verbal Autopsy Questionnaire.
29 May 2013	Modified the testing algorithm for the virological-confirmation by adding the dengue screen reverse transcriptase polymerase chain reaction (RT-PCR) and the Simplexa RT-PCR, assessment of the CYD dengue vaccine in preventing symptomatic virologically-confirmed dengue cases; The study objectives was revised along with the addition of 'Other Objectives'; The Hospital Phase was extended by 2 years to allow a 5-year follow-up period after the last vaccination; and the addition of use of neutralization antibody assays and analyses in addition to PRNT to characterize the immune response.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported