



Clinical trial results:

Immunogenicity and Safety of Yellow Fever Vaccine (Stamaril®) Administered Concomitantly with Tetravalent Dengue Vaccine in Healthy Toddlers at 12-13 Months of Age in Colombia and Peru

Summary

EudraCT number	2014-001714-26
Trial protocol	Outside EU/EEA
Global end of trial date	02 September 2013

Results information

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

Trial information

Trial identification

Sponsor protocol code	CYD29
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01436396
WHO universal trial number (UTN)	U1111-1116-4913

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, 598 2710 3710 X109, betzana.zambrano@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur SA, 598 2710 3710 X109, betzana.zambrano@sanofipasteur.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-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	25 November 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of the immune response against Yellow Fever (YF) in Flavivirus (FV)-naïve subjects at baseline receiving one dose of Stamaril vaccine administered concomitantly with the first dose of CYD dengue vaccine compared to subjects receiving one dose of Stamaril vaccine concomitantly with placebo.

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	07 September 2011
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	Peru: 320
Country: Number of subjects enrolled	Colombia: 467
Worldwide total number of subjects	787
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)	787
Children (2-11 years)	0

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 07 September 2011 to 08 March 2012 at 2 clinical sites (1 in Colombia and 1 in Peru).

Pre-assignment

Screening details:

A total of 792 subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled and randomized; 787 subjects were vaccinated.

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:

To ensure that objective safety data were obtained, the trial was designed using an observer-blind methodology since the products were visually different and may be recognized. For first trial vaccination (V01), the person who administered the injections knew which products were administered while neither the subject or parent nor the Investigator in charge of safety evaluation knew which products were administered.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Subjects received the Stamaril vaccine and the CYD dengue vaccine at enrollment (M0) at 12 to 13 months, measles, mumps, rubella (MMR) vaccine, pneumococcal conjugated vaccine, and hepatitis A vaccine (M1) at 13 to 14 months, CYD dengue vaccine (M6) at 18 to 19 months, diphtheria, tetanus, acellular pertussis, inactivated polio and Haemophilus influenza type b (DTaP-IPV//Hib) (M7) at 19 to 20 months, CYD dengue vaccine (M12) at 24 to 25 months, and hepatitis A vaccine (M13) at 25 to 26 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 in the deltoid region of the upper arm, 1 injection each at 0, 6, and 12 months.

Investigational medicinal product name	Yellow Fever vaccine (Stamaril®)
Investigational medicinal product code	105
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous in the deltoid region of the upper arm, 1 injection at Month 0.

Arm title	Group 2
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Arm description:

Subjects received the Stamaril vaccine and placebo at enrollment (M0) at 12 to 13 months of age, MMR vaccine, pneumococcal conjugated vaccine, and hepatitis A vaccine (M1) at 13 to 14 months, CYD dengue vaccine (M6) at 18 to 19 months, DTaP-IPV//Hib (M7) at 19 to 20 months, CYD dengue vaccine

(M12) at 24 to 25 months, and hepatitis A vaccine (M13) at 25 to 26 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 in the deltoid region of the upper arm, 2 injections each at 6 and 12 months.

Investigational medicinal product name	Yellow Fever vaccine (Stamaril®)
Investigational medicinal product code	105
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous in the deltoid region of the upper arm, 1 injection at Month 0.

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 in the deltoid region of the upper arm, 1 injection at Month 0.

Number of subjects in period 1	Group 1	Group 2
Started	394	393
Completed	362	351
Not completed	32	42
Consent withdrawn by subject	19	29
Adverse event, non-fatal	1	2
Serious adverse event	2	3
Lost to follow-up	3	3
Protocol deviation	7	5

Baseline characteristics

Reporting groups

Reporting group title	Group 1
Reporting group description:	
Subjects received the Stamaril vaccine and the CYD dengue vaccine at enrollment (M0) at 12 to 13 months, measles, mumps, rubella (MMR) vaccine, pneumococcal conjugated vaccine, and hepatitis A vaccine (M1) at 13 to 14 months, CYD dengue vaccine (M6) at 18 to 19 months, diphtheria, tetanus, acellular pertussis, inactivated polio and Haemophilus influenza type b (DTaP-IPV//Hib) (M7) at 19 to 20 months, CYD dengue vaccine (M12) at 24 to 25 months, and hepatitis A vaccine (M13) at 25 to 26 months.	
Reporting group title	Group 2
Reporting group description:	
Subjects received the Stamaril vaccine and placebo at enrollment (M0) at 12 to 13 months of age, MMR vaccine, pneumococcal conjugated vaccine, and hepatitis A vaccine (M1) at 13 to 14 months, CYD dengue vaccine (M6) at 18 to 19 months, DTaP-IPV//Hib (M7) at 19 to 20 months, CYD dengue vaccine (M12) at 24 to 25 months, and hepatitis A vaccine (M13) at 25 to 26 months.	

Reporting group values	Group 1	Group 2	Total
Number of subjects	394	393	787
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)	394	393	787
Children (2-11 years)	0	0	0
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: months			
arithmetic mean	12.2	12.2	
standard deviation	± 0.25	± 0.25	-
Gender categorical			
Units: Subjects			
Female	198	203	401
Male	196	190	386

End points

End points reporting groups

Reporting group title	Group 1
Reporting group description:	
Subjects received the Stamaril vaccine and the CYD dengue vaccine at enrollment (M0) at 12 to 13 months, measles, mumps, rubella (MMR) vaccine, pneumococcal conjugated vaccine, and hepatitis A vaccine (M1) at 13 to 14 months, CYD dengue vaccine (M6) at 18 to 19 months, diphtheria, tetanus, acellular pertussis, inactivated polio and Haemophilus influenza type b (DTaP-IPV//Hib) (M7) at 19 to 20 months, CYD dengue vaccine (M12) at 24 to 25 months, and hepatitis A vaccine (M13) at 25 to 26 months.	
Reporting group title	Group 2
Reporting group description:	
Subjects received the Stamaril vaccine and placebo at enrollment (M0) at 12 to 13 months of age, MMR vaccine, pneumococcal conjugated vaccine, and hepatitis A vaccine (M1) at 13 to 14 months, CYD dengue vaccine (M6) at 18 to 19 months, DTaP-IPV//Hib (M7) at 19 to 20 months, CYD dengue vaccine (M12) at 24 to 25 months, and hepatitis A vaccine (M13) at 25 to 26 months.	

Primary: Percentage of Non-immune Subjects With Seroconversion Against Yellow Fever Antigen After Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo

End point title	Percentage of Non-immune Subjects With Seroconversion Against Yellow Fever Antigen After Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo
End point description:	
Neutralizing antibodies against yellow fever (YF) were assessed using a YF virus plaque reduction neutralization test (YF PRNT50) assay. Seroconversion was defined as YF antibodies ≥ 10 (1/dil) in flavivirus non-immune subjects.	
End point type	Primary
End point timeframe:	
28 days Post-Injection 1	

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	296	299		
Units: Percentage of subjects				
number (not applicable)				
Seroconversion	100	99.7		

Statistical analyses

Statistical analysis title	Non-inferiority (Group 1 - Group 2)
Statistical analysis description:	
Non-inferiority of YF seroconversion rate was assessed 28 days post-Stamaril/CYD dengue vaccine (Group 1) or post-Stamaril/placebo (Group 2).	
Comparison groups	Group 1 v Group 2

Number of subjects included in analysis	595
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Parameter estimate	Difference in Grp 1 - Grp 2 (percentage)
Point estimate	0.334
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.976
upper limit	1.87

Notes:

[1] - The non-inferiority will be demonstrated if the lower limit of the 95% CI is greater than -10. The difference in percentage of seroconversion rates between group 1 and 2 is based on the Wilson score (without continuity adjustment) 95% two-sided confidence intervals.

Secondary: Percentage of All Subjects With Seroconversion Against Yellow Fever Antigen After Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo

End point title	Percentage of All Subjects With Seroconversion Against Yellow Fever Antigen After Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo
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End point description:

Neutralizing antibodies against yellow fever (YF) were assessed using a YF virus plaque reduction neutralization test (YF PRNT50) assay. Seroconversion was defined as YF antibodies ≥ 10 (1/dil) in subjects YF-seronegative at baseline or 4-fold increase from pre- to post-YF antibody titers in subjects YF-seropositive at baseline.

End point type	Secondary
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End point timeframe:

28 days Post-Injection 1

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	381	377		
Units: Percentage of subjects				
number (not applicable)				
Seroconversion	98.7	99.7		

Statistical analyses

Statistical analysis title	Non-inferiority (Group 1 - Group 2)
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Statistical analysis description:

Non-inferiority of YF seroconversion rate was assessed 28 days post-Stamaril/CYD dengue vaccine (Group 1) or post-Stamaril/placebo (Group 2).

Comparison groups	Group 1 v Group 2
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Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
Parameter estimate	Difference in Grp 1 - Grp 2 (percentage)
Point estimate	-1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.81
upper limit	0.383

Notes:

[2] - The non-inferiority will be demonstrated if the lower limit of the 95% CI is greater than -10. The difference in percentage of seroconversion rates between group 1 and 2 is based on the Wilson score (without continuity adjustment) 95% two-sided confidence intervals.

Secondary: Geometric Mean Titers (GMTs) of Yellow Fever Antibodies In All Subjects Following Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines

End point title	Geometric Mean Titers (GMTs) of Yellow Fever Antibodies In All Subjects Following Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines
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End point description:

Geometric mean titers against yellow fever (YF) were assessed using a YF virus plaque reduction neutralization test (YF PRNT50) assay.

End point type	Secondary
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End point timeframe:

Pre-Injection 1 and Post-Injection 1

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	381	377		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Pre-Injection 1	5.64 (5.41 to 5.89)	5.67 (5.42 to 5.93)		
Post-Injection 1	369 (322 to 423)	423 (375 to 478)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titer Ratios (GMTRs) of Yellow Fever Antibodies In All Subjects Following Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines

End point title	Geometric Mean Titer Ratios (GMTRs) of Yellow Fever Antibodies In All Subjects Following Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines
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End point description:

Geometric mean titer ratios against yellow fever (YF) were assessed using a YF virus plaque reduction neutralization test (YF PRNT50) assay.

End point type	Secondary
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End point timeframe:

Pre-Injection 1 and Post-Injection 1

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	381	377		
Units: Titer ratios				
geometric mean (confidence interval 95%)				
Post-Injection 1/Pre-Injection 1	35.1 (30.5 to 40.4)	39.8 (35.3 to 45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of All Subjects With Yellow Fever Antibody Titers of ≥ 10 (1/dil) Before and After Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo

End point title	Percentage of All Subjects With Yellow Fever Antibody Titers of ≥ 10 (1/dil) Before and After Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo
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End point description:

Neutralizing antibodies against yellow fever (YF) were assessed using a YF virus plaque reduction neutralization test (YF PRNT50) assay. Seroconversion was defined as YF antibodies ≥ 10 (1/dil) regardless of the flavivirus status of subjects at baseline.

End point type	Secondary
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End point timeframe:

Pre-Injection 1 and Post-Injection 1

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	381	377		
Units: Percentage of subjects				
number (not applicable)				
Pre-Injection 1	9	9		
Post-Injection 1	99.5	99.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs) of Dengue Virus Antibodies Following Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines, Followed by CYD Dengue Vaccines

End point title	Geometric Mean Titers (GMTs) of Dengue Virus Antibodies Following Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines, Followed by CYD Dengue Vaccines
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End point description:

Geometric mean titers against each serotype with the parental dengue virus strains were assessed using a dengue plaque reduction neutralization test (PRNT) assay.

End point type	Secondary
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End point timeframe:

Pre-Injection 1 and Post-Injections 2 and 3

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	113		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
CYD dengue Serotype 1; Pre-Injection 1	5.08 (4.92 to 5.25)	5 (5 to 5)		
CYD dengue Serotype 1; Post-Injection 2	47.3 (38.9 to 57.5)	11.8 (9.82 to 14.1)		
CYD dengue Serotype 1; Post-Injection 3	89 (76.4 to 104)	61.3 (52.5 to 71.5)		
CYD dengue Serotype 2; Pre-Injection 1	5.1 (4.96 to 5.23)	5 (5 to 5)		
CYD dengue Serotype 2; Post-Injection 2	95.5 (78 to 117)	41.1 (33.2 to 51)		
CYD dengue Serotype 2; Post-Injection 3	173 (142 to 211)	150 (127 to 177)		
CYD dengue Serotype 3; Pre-Injection 1	5.05 (4.95 to 5.16)	5.18 (5 to 5.37)		
CYD dengue Serotype 3; Post-Injection 2	118 (101 to 137)	43.4 (36 to 52.3)		
CYD dengue Serotype 3; Post-Injection 3	181 (158 to 207)	155 (136 to 176)		
CYD dengue Serotype 4; Pre-Injection 1	5 (5 to 5)	5.05 (4.96 to 5.14)		
CYD dengue Serotype 4; Post-Injection 2	68.1 (54.6 to 84.9)	29.8 (22.1 to 40.2)		
CYD dengue Serotype 4; Post-Injection 3	74 (61.3 to 89.4)	74.6 (62.5 to 89.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titer Ratios (GMTRs) of Dengue Virus Antibodies Following Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines

End point title	Geometric Mean Titer Ratios (GMTRs) of Dengue Virus Antibodies Following Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines
End point description:	Geometric mean titer ratios against each serotype with the parental dengue virus strains were assessed using a dengue plaque reduction neutralization test (PRNT) assay.
End point type	Secondary
End point timeframe:	Pre-Injection 1 and Post-Injections 2 and 3

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	113		
Units: Titer ratios				
geometric mean (confidence interval 95%)				
CYD dengue Serotype 1; Post-Inj. 2/Pre-Inj. 1	4.78 (3.91 to 5.84)	1.15 (0.973 to 1.37)		
CYD dengue Serotype 1; Post-Inj. 3/Pre-Inj. 1	8.82 (7.55 to 10.3)	6.14 (5.26 to 7.18)		
CYD dengue Serotype 2; Post-Inj. 2/Pre-Inj. 1	9.55 (7.75 to 11.8)	3.86 (3.15 to 4.72)		
CYD dengue Serotype 2; Post-Inj. 3/Pre-Inj. 1	16.7 (13.7 to 20.4)	15.2 (12.8 to 18.1)		
CYD dengue Serotype 3; Post-Inj. 2/Pre-Inj. 1	11.6 (9.98 to 13.5)	4.16 (3.46 to 5)		
CYD dengue Serotype 3; Post-Inj. 3/Pre-Inj. 1	18 (15.6 to 20.8)	15.4 (13.5 to 17.6)		
CYD dengue Serotype 4; Post-Inj. 2/Pre-Inj. 1	6.82 (5.44 to 8.55)	2.89 (2.15 to 3.89)		
CYD dengue Serotype 4; Post-Inj. 3/Pre-Inj. 1	7.26 (6.02 to 8.77)	7.44 (6.24 to 8.88)		

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 After Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines

End point title	Percentage of Subjects With Antibody Titer ≥ 10 (1/dil) Against Each Serotype with the Parental Dengue Virus Strains After Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines
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End point description:

Neutralizing antibodies against each serotype with the parental dengue virus strains were assessed using a dengue plaque reduction neutralization test (PRNT) assay. Seroconversion was defined as antibody titers ≥ 10 (1/dil) against each serotype with the parental dengue virus strains.

End point type	Secondary
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End point timeframe:

Pre-Injection 1 and Post-Injections 2 and 3

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	113		
Units: Percentage of subjects				
number (not applicable)				
CYD dengue Serotype 1; Pre-Injection 1	0.9	0		
CYD dengue Serotype 1; Post-Injection 2	92	51.3		
CYD dengue Serotype 1; Post-Injection 3	100	97.2		
CYD dengue Serotype 2; Pre-Injection 1	1.8	0		
CYD dengue Serotype 2; Post-Injection 2	97.3	86.7		
CYD dengue Serotype 2; Post-Injection 3	100	100		
CYD dengue Serotype 3; Pre-Injection 1	0.9	3.7		
CYD dengue Serotype 3; Post-Injection 2	100	90.3		
CYD dengue Serotype 3; Post-Injection 3	100	100		
CYD dengue Serotype 4; Pre-Injection 1	0	0.9		
CYD dengue Serotype 4; Post-Injection 2	91.2	68.1		
CYD dengue Serotype 4; Post-Injection 3	97.3	98.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Antibody Titer ≥ 10 (1/dil) Against At Least 1, 2, 3, or 4 Serotypes with the Parental Dengue Virus Strains After Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines

End point title	Percentage of Subjects With Antibody Titer ≥ 10 (1/dil) Against At Least 1, 2, 3, or 4 Serotypes with the Parental Dengue Virus Strains After Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines
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End point description:

Neutralizing antibodies against at least 1, 2, 3, or 4 serotypes with the parental dengue virus strains were assessed using a dengue plaque reduction neutralization test (PRNT) assay.

End point type	Secondary
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End point timeframe:

Pre-Injection 1 and Post-Injections 2 and 3

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	113		
Units: Percentage of subjects				
number (not applicable)				
CYD dengue, At least 1 serotype; Pre-Injection 1	3.6	4.5		
CYD dengue, At least 1 serotype; Post-Injection 2	100	93.8		
CYD dengue, At least 1 serotype; Post-Injection 3	100	100		
CYD dengue, At least 2 serotypes; Pre-Injection 1	0	0		
CYD dengue, At least 2 serotypes; Post-Injection 2	100	87.6		
CYD dengue, At least 2 serotypes; Post-Injection 3	100	100		
CYD dengue, At least 3 serotypes; Pre-Injection 1	0	0		
CYD dengue, At least 3 serotypes; Post-Injection 2	94.7	73.5		
CYD dengue, At least 3 serotypes; Post-Injection 3	100	98.1		
CYD dengue, All 4 serotypes; Pre-Injection 1	0	0		
CYD dengue, All 4 serotypes; Post-Injection 2	85.8	41.6		
CYD dengue, All 4 serotypes; Post-Injection 3	97.3	97.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers of Dengue Virus Antibodies of Flavivirus-immune Subjects Following Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines, Followed by CYD Dengue Vaccin

End point title	Geometric Mean Titers of Dengue Virus Antibodies of Flavivirus-immune Subjects Following Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines, Followed by CYD Dengue Vaccin
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End point description:

Geometric mean titers against each serotype with the parental dengue virus strains were assessed using a dengue plaque reduction neutralization test (PRNT) assay. Flavivirus-immune subjects at baseline were defined as those subjects with ≥ 10 (1/dil) for at least 1 serotype with the parental dengue virus strain or for YF virus.

End point type	Secondary
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End point timeframe:

Pre-Injection 1 and Post-Injections 2 and 3

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	14		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
CYD dengue Serotype 1; Pre-Injection 1	5.96 (4.01 to 8.87)	5 (5 to 5)		
CYD dengue Serotype 1; Post-Injection 2	52.5 (25 to 110)	17 (7.63 to 38)		
CYD dengue Serotype 1; Post-Injection 3	81.7 (47.3 to 141)	59.5 (44.6 to 79.5)		
CYD dengue Serotype 2; Pre-Injection 1	6.14 (4.5 to 8.38)	5 (5 to 5)		
CYD dengue Serotype 2; Post-Injection 2	72.4 (47.4 to 111)	74.3 (27.6 to 200)		
CYD dengue Serotype 2; Post-Injection 3	110 (75.5 to 160)	133 (95.7 to 186)		
CYD dengue Serotype 3; Pre-Injection 1	5.74 (4.15 to 7.94)	6.75 (5.05 to 9.03)		
CYD dengue Serotype 3; Post-Injection 2	102 (54.8 to 189)	95.8 (61.3 to 150)		
CYD dengue Serotype 3; Post-Injection 3	143 (89.7 to 227)	126 (91.7 to 173)		
CYD dengue Serotype 4; Pre-Injection 1	5 (5 to 5)	5.41 (4.55 to 6.43)		
CYD dengue Serotype 4; Post-Injection 2	87.1 (36 to 210)	109 (44.7 to 265)		
CYD dengue Serotype 4; Post-Injection 3	77.1 (24 to 248)	74.3 (40.9 to 135)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers of Dengue Virus Antibodies of Flavivirus-Naïve Subjects Following Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines, Followed by CYD Dengue Vaccines

End point title	Geometric Mean Titers of Dengue Virus Antibodies of Flavivirus-Naïve Subjects Following Vaccination With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines, Followed by CYD Dengue Vaccines
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End point description:

Geometric mean titers against each serotype with the parental dengue virus strains were assessed using a dengue plaque reduction neutralization test (PRNT) assay. Flavivirus-non-immune (naïve) subjects at baseline were defined as those subjects with <10 (1/dil) for all serotypes with parental dengue virus strains and for YF virus.

End point type	Secondary
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End point timeframe:

Pre-Injection 1 and Post-Injections 2 and 3

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	90		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
CYD dengue Serotype 1; Pre-Injection 1	5 (5 to 5)	5 (5 to 5)		
CYD dengue Serotype 1; Post-Injection 2	45.9 (37 to 57)	11.4 (9.42 to 13.7)		
CYD dengue Serotype 1; Post-Injection 3	86.6 (73 to 103)	61.8 (51.5 to 74.3)		
CYD dengue Serotype 2; Pre-Injection 1	5 (5 to 5)	5 (5 to 5)		
CYD dengue Serotype 2; Post-Injection 2	99 (78 to 126)	39 (31.4 to 48.5)		
CYD dengue Serotype 2; Post-Injection 3	174 (139 to 218)	157 (129 to 192)		
CYD dengue Serotype 3; Pre-Injection 1	5 (5 to 5)	5 (5 to 5)		
CYD dengue Serotype 3; Post-Injection 2	118 (101 to 139)	37.9 (30.8 to 46.8)		
CYD dengue Serotype 3; Post-Injection 3	184 (158 to 214)	160 (138 to 187)		
CYD dengue Serotype 4; Pre-Injection 1	5 (5 to 5)	5 (5 to 5)		
CYD dengue Serotype 4; Post-Injection 2	66.4 (51.8 to 85.1)	24 (17.4 to 33.2)		
CYD dengue Serotype 4; Post-Injection 3	73 (60 to 88.7)	72.2 (59.1 to 88.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Flavivirus-immune Subjects With Antibody Titer ≥ 10 (1/dil) Against Each Serotype with the Parental Dengue Virus Strains After Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines

End point title	Percentage of Flavivirus-immune Subjects With Antibody Titer ≥ 10 (1/dil) Against Each Serotype with the Parental Dengue Virus Strains After Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines
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End point description:

Neutralizing antibodies against each serotype with the parental dengue virus strains were assessed using a dengue plaque reduction neutralization test (PRNT) assay. Flavivirus-immune subjects at baseline were defined as those subjects with ≥ 10 (1/dil) for at least 1 serotype with the parental dengue virus strain or for YF virus.

End point type	Secondary
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End point timeframe:

Pre-Injection 1 and Post-Injections 2 and 3

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	14		
Units: Percentage of subjects				
number (not applicable)				
CYD dengue Serotype 1; Pre-Injection 1	10	0		
CYD dengue Serotype 1; Post-Injection 2	90	57.1		
CYD dengue Serotype 1; Post-Injection 3	100	100		
CYD dengue Serotype 2; Pre-Injection 1	20	0		
CYD dengue Serotype 2; Post-Injection 2	100	92.9		
CYD dengue Serotype 2; Post-Injection 3	100	100		
CYD dengue Serotype 3; Pre-Injection 1	12.5	30.8		
CYD dengue Serotype 3; Post-Injection 2	100	100		
CYD dengue Serotype 3; Post-Injection 3	100	100		
CYD dengue Serotype 4; Pre-Injection 1	0	7.7		
CYD dengue Serotype 4; Post-Injection 2	90	92.9		
CYD dengue Serotype 4; Post-Injection 3	88.9	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Flavivirus-naïve Subjects With Antibody Titer ≥ 10 (1/dil) Against Each Serotype with the Parental Dengue Virus Strains After Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines

End point title	Percentage of Flavivirus-naïve Subjects With Antibody Titer ≥ 10 (1/dil) Against Each Serotype with the Parental Dengue Virus Strains After Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines
End point description:	
Neutralizing antibodies against each serotype with the parental dengue virus strains were assessed using a dengue plaque reduction neutralization test (PRNT) assay. Flavivirus-non-immune (naïve) subjects at baseline were defined as those subjects with <10 (1/dil) for all serotypes with parental dengue virus strains and for YF virus.	
End point type	Secondary
End point timeframe:	
Pre-Injection 1 and Post-Injections 2 and 3	

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	90		
Units: Percentage of subjects				
number (not applicable)				
CYD dengue Serotype 1; Pre-Injection 1	0	0		
CYD dengue Serotype 1; Post-Injection 2	92.6	51.1		
CYD dengue Serotype 1; Post-Injection 3	100	96.5		
CYD dengue Serotype 2; Pre-Injection 1	0	0		
CYD dengue Serotype 2; Post-Injection 2	96.8	86.7		
CYD dengue Serotype 2; Post-Injection 3	100	100		
CYD dengue Serotype 3; Pre-Injection 1	0	0		
CYD dengue Serotype 3; Post-Injection 2	100	87.8		
CYD dengue Serotype 3; Post-Injection 3	100	100		
CYD dengue Serotype 4; Pre-Injection 1	0	0		
CYD dengue Serotype 4; Post-Injection 2	90.4	63.3		
CYD dengue Serotype 4; Post-Injection 3	97.8	97.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions Following Any and Each Injection With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines

End point title	Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions Following Any and Each Injection With Yellow Fever Vaccine Concomitantly with Either CYD Dengue Vaccine or a Placebo, Followed by CYD Dengue Vaccines
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End point description:

Solicited injection site reactions: Tenderness, Erythema, and Swelling. Solicited systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost and Irritability. Grade 3 Solicited injection site reactions: Tenderness, Cries when injected limb is moved or the movement of the injected limb is reduced; Erythema and Swelling, ≥ 50 mm. Grade 3 Solicited systemic reactions: Fever, $>39.5^{\circ}\text{C}$; Vomiting, ≥ 6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, >3 hours; Drowsiness, Sleeping most of the time or difficult to wake up; Appetite lost, Refuses ≥ 3 feeds/meals or refuses most feeds/meals; Irritability, Inconsolable.

End point type	Secondary
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End point timeframe:

Day 0 up to Day 14 post-Injection 3

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	394	393		
Units: Percentage of subjects				
number (not applicable)				
Inj. site Tenderness for Stamaril; Post-Any Inj.	25.4	17.6		
Grd 3 Inj. site Tenderness, Stamaril; Post-Any Inj	0.3	0.3		
Inj. site Tenderness for CYD dengue; Post-Any Inj.	36.5	28.9		
Grd 3 Inj site Tenderness, CYD dengue;Post-Any Inj	0.3	0		
Inj. site Tenderness for placebo; Post-Any Inj.	0	19.7		
Grd 3 Inj. site Tenderness, placebo; Post-Any Inj.	0	0.3		
Inj. site Erythema for Stamaril; Post-Any Inj.	8.3	9.8		
Grd 3 Inj. site Erythema, Stamaril; Post-Any Inj.	0	0		
Inj. site Erythema for CYD dengue; Post-Any Inj.	12.7	8.8		
Grd 3 Inj. site Erythema, CYD dengue; Post-Any Inj	0	0		
Inj. site Erythema for placebo; Post-Any Inj.	0	10.9		
Grd 3 Inj. site Erythema for placebo; Post-Any Inj	0	0		
Inj. site Swelling for Stamaril; Post-Any Inj.	4.7	4.4		
Grd 3 Inj. site Swelling, Stamaril; Post-Any Inj.	0	0		
Inj. site Swelling for CYD dengue; Post-Any Inj.	7.5	6.1		
Grd 3 Inj. site Swelling, CYD dengue; Post-Any Inj	0	0		
Inj. site Swelling for placebo; Post-Any Inj.	0	4.9		
Grd 3 Inj. site Swelling for placebo; Post-Any Inj	0	0		
Inj. site Tenderness for Stamaril; Post-Inj. 1	25.4	17.6		
Grd 3 Inj. site Tenderness, Stamaril; Post-Inj. 1	0.3	0.3		
Inj. site Tenderness for CYD dengue; Post-Inj. 1	24.9	0		
Grd 3 Inj. site Tenderness, CYD dengue; Post-Inj 1	0	0		
Inj. site Tenderness for placebo; Post-Inj. 1	0	19.7		
Grd 3 Inj. site Tenderness, placebo; Post-Inj. 1	0	0.3		
Inj. site Erythema for Stamaril; Post-Inj. 1	8.3	9.8		

Grd 3 Inj. site Erythema for Stamaril; Post-Inj. 1	0	0		
Inj. site Erythema for CYD dengue; Post-Inj. 1	8.8	0		
Grd 3 Inj. site Erythema, CYD dengue; Post-Inj. 1	0	0		
Inj. site Erythema for placebo; Post-Inj. 1	0	10.9		
Grd 3 Inj. site Erythema for placebo; Post-Inj. 1	0	0		
Inj. site Swelling for Stamaril; Post-Inj. 1	4.7	4.4		
Grd 3 Inj. site Swelling for Stamaril; Post-Inj. 1	0	0		
Inj. site Swelling for CYD dengue; Post- Inj. 1	4.7	0		
Grd 3 Inj. site Swelling, CYD dengue; Post-Inj. 1	0	0		
Inj. site Swelling for placebo; Post-Inj. 1	0	4.9		
Grd 3 Inj. site Swelling for placebo; Post-Inj. 1	0	0		
Inj. site Tenderness for CYD dengue; Post-Inj. 2	17	20.4		
Grd 3 Inj. site Tenderness, CYD dengue; Post-Inj 2	0	0		
Inj. site Erythema for CYD dengue; Post-Inj. 2	5.1	8		
Grd 3 Inj. site Erythema, CYD dengue; Post-Inj. 2	0	0		
Inj. site Swelling for CYD dengue; Post- Inj. 2	2.7	4.7		
Grd 3 Inj. site Swelling, CYD dengue; Post-Inj. 2	0	0		
Inj. site Tenderness for CYD dengue; Post-Inj. 3	14.6	16.3		
Grd 3 Inj. site Tenderness, CYD dengue; Post-Inj 3	0.3	0		
Inj. site Erythema for CYD dengue; Post-Inj. 3	3.6	4.2		
Grd 3 Inj. site Erythema, CYD dengue; Post-Inj. 3	0	0		
Inj. site Swelling for CYD dengue; Post- Inj. 3	1.6	2.8		
Grd 3 Inj. site Swelling, CYD dengue; Post-Inj. 3	0	0		
Fever; Post-Any Injection	48.1	40.3		
Grade 3 Fever; Post-Any Injection	1.3	0.8		
Vomiting; Post-Any Injection	30.6	27.2		
Grade 3 Vomiting; Post-Any Injection	1.3	2.1		
Crying abnormal; Post-Any Injection	47.2	44		
Grade 3 Crying abnormal; Post-Any Injection	0.5	1.3		
Drowsiness; Post-Any Injection	36.3	33.9		
Grade 3 Drowsiness; Post-Any Injection	0.5	0		
Appetite lost; Post-Any Injection	54.7	50		
Grade 3 Appetite lost; Post-Any Injection	4.7	3.6		
Irritability; Post-Any Injection	46.4	46.4		
Grade 3 Irritability; Post-Any Injection	1.6	1.6		
Fever; Post-Injection 1	26.7	16.5		

Grade 3 Fever; Post-Injection 1	1.1	0.3		
Vomiting; Post-Injection 1	16.1	17.1		
Grade 3 Vomiting; Post-Injection 1	0.5	1		
Crying abnormal; Post-Injection 1	32.9	32.1		
Grade 3 Crying abnormal; Post-Injection 1	0.5	1.3		
Drowsiness; Post-Injection 1	24.4	22		
Grade 3 Drowsiness; Post-Injection 1	0.5	0		
Appetite lost; Post-Injection 1	39.6	33.7		
Grade 3 Appetite lost; Post-Injection 1	4.4	3.1		
Irritability; Post-Injection 1	38.6	34.7		
Grade 3 Irritability; Post-Injection 1	1.6	1.3		
Fever; Post-Injection 2	21.2	22.2		
Grade 3 Fever; Post-Injection 2	0	0.3		
Vomiting; Post-Injection 2	12.4	8.8		
Grade 3 Vomiting; Post-Injection 2	0.5	0.6		
Crying abnormal; Post-Injection 2	19.7	21.8		
Grade 3 Crying abnormal; Post-Injection 2	0	0		
Drowsiness; Post-Injection 2	12.7	16.5		
Grade 3 Drowsiness; Post-Injection 2	0	0		
Appetite lost; Post-Injection 2	27	23.1		
Grade 3 Appetite lost; Post-Injection 2	0.3	0.3		
Irritability; Post-Injection 2	17.3	22.3		
Grade 3 Irritability; Post-Injection 2	0	0		
Fever; Post-Injection 3	20.3	17.8		
Grade 3 Fever; Post-Injection 3	0.3	0.3		
Vomiting; Post-Injection 3	7.4	7.3		
Grade 3 Vomiting; Post-Injection 3	0.3	0.6		
Crying abnormal; Post-Injection 3	15.1	14.6		
Grade 3 Crying abnormal; Post-Injection 3	0	0		
Drowsiness; Post-Injection 3	11.3	10.7		
Grade 3 Drowsiness; Post-Injection 3	0	0		
Appetite lost; Post-Injection 3	19.8	18.6		
Grade 3 Appetite lost; Post-Injection 3	0	0.3		
Irritability; Post-Injection 3	14.3	16.1		
Grade 3 Irritability; Post-Injection 3	0	0.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from Day 0 (post-vaccination) up to 6 months post-Injection 3.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.4
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Reporting groups

Reporting group title	Group 1
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Reporting group description:

Subjects received the Stamaril vaccine and the first dose of the CYD dengue vaccine at enrollment (Month 0) at 12 to 13 months of age, measles, mumps, rubella (MMR) vaccine, pneumococcal conjugated vaccine, and hepatitis A vaccine (Month 1) at 13 to 14 months of age, second dose of CYD dengue vaccine (Month 6) at 18 to 19 months of age, diphtheria, tetanus, acellular pertussis, inactivated polio and Haemophilus influenza type b (DTaP-IPV//Hib) (Month 7) at 19 to 20 months of age, third dose of the CYD dengue vaccine (Month 12) at 24 to 25 months of age, and hepatitis A vaccine (Month 13) at 25 to 26 months of age.

Reporting group title	Group 2
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Reporting group description:

Subjects received the Stamaril vaccine and placebo at enrollment (Month 0) at 12 to 13 months of age, measles, mumps, rubella (MMR) vaccine, pneumococcal conjugated vaccine, and hepatitis A vaccine (Month 1) at 13 to 14 months of age, first dose of CYD dengue vaccine (Month 6) at 18 to 19 months of age, diphtheria, tetanus, acellular pertussis, inactivated polio and Haemophilus influenza type b (DTaP-IPV//Hib) (Month 7) at 19 to 20 months of age, second dose of the CYD dengue vaccine (Month 12) at 24 to 25 months of age, and hepatitis A vaccine (Month 13) at 25 to 26 months of age.

Serious adverse events	Group 1	Group 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 394 (8.88%)	38 / 393 (9.67%)	
number of deaths (all causes)	0	1	
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 / 394 (0.00%)	1 / 393 (0.25%)	
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 / 394 (0.25%)	0 / 393 (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 / 394 (0.25%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 394 (0.25%)	0 / 393 (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	0 / 394 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue injury			
subjects affected / exposed	0 / 394 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic brain injury			
subjects affected / exposed	0 / 394 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 394 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 393 (0.25%)	
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	6 / 394 (1.52%)	4 / 393 (1.02%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Lymphadenitis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 394 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 393 (0.25%)	
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	0 / 394 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic crisis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 394 (0.25%)	0 / 393 (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	2 / 394 (0.51%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	2 / 394 (0.51%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis orbital			
subjects affected / exposed	0 / 394 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 394 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	1 / 394 (0.25%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 394 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 394 (0.25%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impetigo			
subjects affected / exposed	1 / 394 (0.25%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	0 / 394 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			

subjects affected / exposed	0 / 394 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	12 / 394 (3.05%)	11 / 393 (2.80%)	
occurrences causally related to treatment / all	0 / 16	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 394 (0.00%)	1 / 393 (0.25%)	
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 / 394 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 393 (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	4 / 394 (1.02%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 394 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Malnutrition			

subjects affected / exposed	1 / 394 (0.25%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Group 1	Group 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	211 / 394 (53.55%)	193 / 393 (49.11%)	
Nervous system disorders			
Drowsiness; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed ^[1]	140 / 386 (36.27%)	131 / 386 (33.94%)	
occurrences (all)	182	183	
General disorders and administration site conditions			
Injection site Tenderness for Stamaril vaccine; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed ^[2]	98 / 386 (25.39%)	68 / 386 (17.62%)	
occurrences (all)	98	68	
Injection site Tenderness for CYD dengue vaccine; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed ^[3]	141 / 386 (36.53%)	105 / 363 (28.93%)	
occurrences (all)	212	132	
Injection site Tenderness for placebo; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed ^[4]	0 / 394 (0.00%)	76 / 386 (19.69%)	
occurrences (all)	0	76	
Injection site Erythema for Stamaril vaccine; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed ^[5]	32 / 386 (8.29%)	38 / 386 (9.84%)	
occurrences (all)	32	38	
Injection site Erythema for CYD dengue vaccine; Post-Any Injection			
alternative assessment type:			

Systematic			
subjects affected / exposed ^[6]	49 / 386 (12.69%)	32 / 363 (8.82%)	
occurrences (all)	66	44	
Injection site Erythema for placebo; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed ^[7]	0 / 394 (0.00%)	42 / 386 (10.88%)	
occurrences (all)	0	42	
Injection site Swelling for CYD dengue vaccine; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed ^[8]	29 / 386 (7.51%)	22 / 363 (6.06%)	
occurrences (all)	34	27	
Fever; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed ^[9]	185 / 385 (48.05%)	155 / 385 (40.26%)	
occurrences (all)	248	199	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	61 / 394 (15.48%)	59 / 393 (15.01%)	
occurrences (all)	73	71	
Vomiting; Post-Any Injection			
alternative assessment type: Systematic			
subjects affected / exposed ^[10]	118 / 386 (30.57%)	105 / 386 (27.20%)	
occurrences (all)	135	124	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	26 / 394 (6.60%)	18 / 393 (4.58%)	
occurrences (all)	29	21	
Cough			
subjects affected / exposed	24 / 394 (6.09%)	22 / 393 (5.60%)	
occurrences (all)	27	24	
Psychiatric disorders			
Crying abnormal; Post-Any Injection			
alternative assessment type: Systematic			

subjects affected / exposed ^[11]	182 / 386 (47.15%)	170 / 386 (44.04%)	
occurrences (all)	255	255	
Irritability; Post-Any Injection alternative assessment type: Systematic			
subjects affected / exposed ^[12]	179 / 386 (46.37%)	179 / 386 (46.37%)	
occurrences (all)	265	272	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	44 / 394 (11.17%)	43 / 393 (10.94%)	
occurrences (all)	46	49	
Nasopharyngitis			
subjects affected / exposed	118 / 394 (29.95%)	120 / 393 (30.53%)	
occurrences (all)	140	140	
Pharyngitis			
subjects affected / exposed	73 / 394 (18.53%)	52 / 393 (13.23%)	
occurrences (all)	90	65	
Metabolism and nutrition disorders			
Appetite lost; Post-Any Injection alternative assessment type: Systematic			
subjects affected / exposed ^[13]	211 / 386 (54.66%)	193 / 386 (50.00%)	
occurrences (all)	325	280	

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 injection; 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 injection; 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 injection; 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 injection; 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 7 days after any injection; 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 7 days after any injection; 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 7 days after any injection; 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 7 days after any injection; 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 solicited adverse event recorded in a diary card within 14 days after any injection; 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 solicited adverse event recorded in a diary card within 14 days after any injection; 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 solicited adverse event recorded in a diary card within 14 days after any injection; 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.

[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: This was a solicited adverse event recorded in a diary card within 14 days after any injection; 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.

[13] - 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 injection; 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
19 September 2011	The Bogoto site initially planned could not participate due to incompleteness of certification with the regulatory process, Peru requested 2 doses of Hepatitis A vaccines should be offered instead of 1 to all subjects as a benefit and the 6-month follow up visit could be a home visit if needed, information regarding the composition and administration of products was reworded to provide more flexibility, minor updates, methodology updates, and process clarification were made, and minor administrative updates including the change of the Regional Director of Clinical Development and Regional Clinical Trial Manager were included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/22863660>