Clinical trial results:
A Controlled Study of the Safety and Immunogenicity of ChimeriVax™ Japanese Encephalitis Vaccine in Thai Toddlers and Children

Summary

EudraCT number	2015-005193-38
Trial protocol	Outside EU/EEA
Global end of trial date	28 May 2013

Results information

Result version number	v1 (current)
This version publication date	18 February 2016
First version publication date	18 February 2016

Trial information

Trial identification

Sponsor protocol code	JEC01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00621764
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	2, avenue Pont Pasteur, Lyon Cedex 07, France, F-69367
Public contact	Medical Director, Sanofi Pasteur SA, 33 4 37 37 5843, Emmanuel.Feroldi@sanofipasteur.com
Scientific contact	Medical Director, Sanofi Pasteur SA, 33 4 37 37 5843, Emmanuel.Feroldi@sanofipasteur.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 May 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

•To describe the safety of a single dose of JE CV in comparison with hepatitis A control vaccine in two age cohorts: children aged 2 to 5 years previously vaccinated with two doses of a mouse-brain-derived inactivated JE vaccine according to the national immunization schedule, and toddlers aged 12 to 24 months previously not vaccinated with any JE vaccine

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	02 March 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Thailand: 301
Worldwide total number of subjects	301
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)	200
Children (2-11 years)	101
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:

The study subjects were enrolled from 02 March 2008 to 06 January 2009 at 3 clinic centers in Thailand.

Pre-assignment

Screening details:

A total of 301 subjects who met all of the inclusion and none of the exclusion criteria were randomized and vaccinated in this study, except for 1 subject in Group 2 who was not vaccinated.

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	JE-CV/Hepatitis A (Group 1)

Arm description:

Children aged 2 to 5 years of age received one dose of Japanese Encephalitis ChimeriVax™ (JE-CV) as first vaccination and one dose of Hepatitis A as second vaccination 28 days apart.

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

Dosage and administration details:

3.0 mL, subcutaneous, 1 injection on Day 0

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

Dosage and administration details:

0.5 mL, intramuscular, 1 injection 28 days after JE-CV vaccine

Arm title	Hepatitis A/JE-CV (Group 2)

Arm description:

Children aged 2 to 5 years of age received one dose of Hepatitis A as first vaccination and one dose of JE-CV as second vaccination 28 days apart.

Arm type	Active comparator
Investigational medicinal product name	Hepatitis A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection on Day 0

Investigational medicinal product name	Japanese encephalitis vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

3.0 mL, subcutaneous, 1 injection 28 days after Hepatitis A vaccine

Arm title	JE-CV/Hepatitis A (Group 3)

Arm description:

Toddlers aged 12 to 24 months of age received one dose of JE-CV as first vaccination and one dose of Hepatitis A as second vaccination 28 days apart.

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

Dosage and administration details:

3.0 mL, subcutaneous, 1 injection on Day 0

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

Dosage and administration details:

0.5 mL, intramuscular, 1 injection 28 days after JE-CV vaccine

Arm title	Hepatitis A/JE-CV (Group 4)

Arm description:

Toddlers aged 12 to 24 months of age received one dose of Hepatitis A as first vaccination and one dose of JE-CV as second vaccination 28 days apart.

Arm type	Active comparator
Investigational medicinal product name	Hepatitis A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection on Day 0

Investigational medicinal product name	Japanese encephalitis vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

3.0 mL, subcutaneous, 1 injection 28 days after Hepatitis A vaccine

Number of subjects in period 1	JE-CV/Hepatitis A (Group 1)	Hepatitis A/JE-CV (Group 2)	JE-CV/Hepatitis A (Group 3)
Started	50	51	101
Completed	50	50	101
Not completed	0	1	0
Not vaccinated	-	1	-
Protocol deviation	-	-	-

Number of subjects in period 1	Hepatitis A/JE-CV (Group 4)
Started	99
Completed	98
Not completed	1
Not vaccinated	-
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	JE-CV/Hepatitis A (Group 1)
Reporting group description:	
Children aged 2 to 5 years of age received one dose of Japanese Encephalitis ChimeriVax™ (JE-CV) as first vaccination and one dose of Hepatitis A as second vaccination 28 days apart.	
Reporting group title	Hepatitis A/JE-CV (Group 2)
Reporting group description:	
Children aged 2 to 5 years of age received one dose of Hepatitis A as first vaccination and one dose of JE-CV as second vaccination 28 days apart.	
Reporting group title	JE-CV/Hepatitis A (Group 3)
Reporting group description:	
Toddlers aged 12 to 24 months of age received one dose of JE-CV as first vaccination and one dose of Hepatitis A as second vaccination 28 days apart.	
Reporting group title	Hepatitis A/JE-CV (Group 4)
Reporting group description:	
Toddlers aged 12 to 24 months of age received one dose of Hepatitis A as first vaccination and one dose of JE-CV as second vaccination 28 days apart.	

Reporting group values	JE-CV/Hepatitis A (Group 1)	Hepatitis A/JE-CV (Group 2)	JE-CV/Hepatitis A (Group 3)
Number of subjects	50	51	101
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	101
Children (2-11 years)	50	51	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: years			
arithmetic mean	2.4	2.5	1.4
standard deviation	± 0.5	± 0.6	± 0.2
Gender categorical Units: Subjects			
Female	17	36	57
Male	33	15	44

Reporting group values	Hepatitis A/JE-CV (Group 4)	Total	
Number of subjects	99	301	
Age categorical Units: Subjects			
In utero	0	0	

Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	99	200	
Children (2-11 years)	0	101	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	1.3		
standard deviation	± 0.2	-	
Gender categorical			
Units: Subjects			
Female	57	167	
Male	42	134	

End points

End points reporting groups

Reporting group title	JE-CV/Hepatitis A (Group 1)
Reporting group description:	
Children aged 2 to 5 years of age received one dose of Japanese Encephalitis ChimeriVax™ (JE-CV) as first vaccination and one dose of Hepatitis A as second vaccination 28 days apart.	
Reporting group title	Hepatitis A/JE-CV (Group 2)
Reporting group description:	
Children aged 2 to 5 years of age received one dose of Hepatitis A as first vaccination and one dose of JE-CV as second vaccination 28 days apart.	
Reporting group title	JE-CV/Hepatitis A (Group 3)
Reporting group description:	
Toddlers aged 12 to 24 months of age received one dose of JE-CV as first vaccination and one dose of Hepatitis A as second vaccination 28 days apart.	
Reporting group title	Hepatitis A/JE-CV (Group 4)
Reporting group description:	
Toddlers aged 12 to 24 months of age received one dose of Hepatitis A as first vaccination and one dose of JE-CV as second vaccination 28 days apart.	

Primary: Number of Subjects With Solicited Injection Site and Systemic Reactions After Injection With Either JE-CV or Hepatitis A Vaccine as First Injection

End point title	Number of Subjects With Solicited Injection Site and Systemic Reactions After Injection With Either JE-CV or Hepatitis A Vaccine as First Injection[1]

End point description:

12 to 24 months – Injection site: Tenderness, Erythema, and Swelling; Systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability. Grade 3: Tenderness, Cries if limb is moved; Erythema and Swelling ≥5 cm; Fever, >39.5°C; Vomiting, ≥6 times/day; Abnormal crying, >3 hours; Drowsiness, Sleeping often; Appetite lost, Refuses ≥3 feeds/meals; Irritability, Inconsolable.

2 to 5 years – Injection site: Pain, Erythema, and Swelling; Systemic reactions: Fever (Temperature), Headache, Malaise, and Myalgia. Grade 3: Pain, Incapacitating; Erythema and Swelling, ≥5 cm; Fever, >39.0°C; Headache, Malaise, and Myalgia, Prevents activities.

End point type	Primary

End point timeframe:

Day 0 up to Day 14 post-vaccination

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	JE-CV/Hepatitis A (Group 1)	Hepatitis A/JE-CV (Group 2)	JE-CV/Hepatitis A (Group 3)	Hepatitis A/JE-CV (Group 4)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50[2]	50[3]	101[4]	99[5]
Units: Number of subjects				
number (not applicable)				
Injection site Pain	15	13	0	0
Grade 3 Injection site Pain	0	0	0	0
Injection site Tenderness	0	0	43	19
Grade 3 Injection site Tenderness	0	0	0	0

Injection site Erythema	7	9	23	16
Grade 3 Injection site Erythema	0	0	0	0
Injection site Swelling	4	5	6	8
Grade 3 Injection site Swelling	0	0	0	0
Fever	8	8	14	18
Grade 3 Fever	1	0	0	0
Headache	7	7	0	0
Grade 3 Headache	0	0	0	0
Malaise	15	13	0	0
Grade 3 Malaise	0	0	0	0
Myalgia	14	8	0	0
Grade 3 Myalgia	0	0	0	0
Vomiting	0	0	21	21
Grade 3 Vomiting	0	0	1	0
Crying abnormal	0	0	24	20
Grade 3 Crying abnormal	0	0	0	0
Drowsiness	0	0	22	13
Grade 3 Drowsiness	0	0	0	0
Appetite lost	0	0	28	32
Grade 3 Appetite lost	0	0	0	2
Irritability	0	0	32	24
Grade 3 Irritability	0	0	0	0

Notes:

[2] - Tenderness, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability were not assessed
[3] - Tenderness, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability were not assessed
[4] - Due to the age, Injection site Pain, Headache, Malaise, and Myalgia were not assessed in this group.
[5] - Due to the age, Injection site Pain, Headache, Malaise, and Myalgia were not assessed in this group.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Solicited Injection Site and Systemic Reactions After Injection With Either JE-CV or Hepatitis A Vaccine as Second Injection

End point title	Number of Subjects With Solicited Injection Site and Systemic Reactions After Injection With Either JE-CV or Hepatitis A Vaccine as Second Injection[6]

End point description:

12 to 24 months – Injection site: Tenderness, Erythema, and Swelling; Systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability. Grade 3: Tenderness, Cries if limb is moved; Erythema and Swelling ≥5 cm; Fever, >39.5°C; Vomiting, ≥6 times/day; Abnormal crying, >3 hours; Drowsiness, Sleeping often; Appetite lost, Refuses ≥3 feeds/meals; Irritability, Inconsolable.

2 to 5 years – Injection site: Pain, Erythema, and Swelling; Systemic reactions: Fever (Temperature), Headache, Malaise, and Myalgia. Grade 3: Pain, Incapacitating; Erythema and Swelling, ≥5 cm; Fever, >39.0°C; Headache, Malaise, and Myalgia, Prevents activities.

End point type	Primary

End point timeframe:

Day 0 up to Day 14 post-vaccination

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine

administered for this outcome.

End point values	JE-CV/Hepatitis A (Group 1)	Hepatitis A/JE-CV (Group 2)	JE-CV/Hepatitis A (Group 3)	Hepatitis A/JE-CV (Group 4)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48[7]	51[8]	101[9]	98[10]
Units: Number of subjects				
number (not applicable)				
Injection site Pain	15	9	0	0
Grade 3 Injection site Pain	0	0	0	0
Injection site Tenderness	0	0	35	20
Grade 3 Injection site Tenderness	0	0	1	0
Injection site Erythema	8	7	23	22
Grade 3 Injection site Erythema	0	0	0	0
Injection site Swelling	8	4	6	11
Grade 3 Injection site Swelling	0	0	0	0
Fever	5	14	23	28
Grade 3 Fever	1	0	1	2
Headache	7	14	0	0
Grade 3 Headache	0	0	0	0
Malaise	13	18	0	0
Grade 3 Malaise	0	0	0	0
Myalgia	7	10	0	0
Grade 3 Myalgia	0	0	0	0
Vomiting	0	0	23	19
Grade 3 Vomiting	0	0	1	1
Crying abnormal	0	0	19	21
Grade 3 Crying abnormal	0	0	2	0
Drowsiness	0	0	17	14
Grade 3 Drowsiness	0	0	0	0
Appetite lost	0	0	26	24
Grade 3 Appetite lost	0	0	2	1
Irritability	0	0	22	24
Grade 3 Irritability	0	0	1	0

Notes:

[7] - Tenderness, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability were not assessed

[8] - Tenderness, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability were not assessed

[9] - Due to the age, Injection site Pain, Headache, Malaise, and Myalgia were not assessed in this group.

[10] - Due to the age, Injection site Pain, Headache, Malaise, and Myalgia were not assessed in this group.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Seroconversion to JE-CV Vaccine Antigens Following Administration of JE-CV Vaccination

End point title	Percentage of Subjects With Seroconversion to JE-CV Vaccine Antigens Following Administration of JE-CV Vaccination

End point description:

JE virus neutralizing antibody measurement was assessed by plaque reduction neutralization test (PRNT50). Seroconversion was defined as subjects with a pre-vaccination titer <10 (1/dil) and post-vaccination titer ≥10 (1/dil), or subjects with pre-vaccination titer ≥10 (1/dil) and 4-fold increase from pre- to post-vaccination.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination) and Day 28 after final vaccination

End point values	JE-CV/Hepatitis A (Group 1)	Hepatitis A/JE-CV (Group 2)	JE-CV/Hepatitis A (Group 3)	Hepatitis A/JE-CV (Group 4)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49	48	87	95
Units: Percentage of subjects				
number (not applicable)				
Homologous virus	89.8	95.8	100	93.2
Genotype I	83.7	93.8	98.8	95.6
Genotype II	83.7	93.8	96.3	95.6
Genotype III	87.8	91.7	100	94.6
Genotype IV	89.8	91.7	74.1	65.6

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Geometric Mean Titers Against JE Antibodies Before and After JE-CV Vaccination

End point title	Summary of Geometric Mean Titers Against JE Antibodies Before and After JE-CV Vaccination

End point description:

JE virus neutralizing antibody measurement was assessed by the PRNT50 assay.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination) and Day 28 after final vaccination

End point values	JE-CV/Hepatitis A (Group 1)	Hepatitis A/JE-CV (Group 2)	JE-CV/Hepatitis A (Group 3)	Hepatitis A/JE-CV (Group 4)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49	48	87	95
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Homologous virus (pre-vaccination)	49.5 (33.9 to 72.1)	40.6 (26.4 to 62.4)	5.78 (5.25 to 6.37)	5.08 (4.92 to 5.24)
Homologous virus (post-vaccination)	1957 (1227 to 3120)	3568 (2361 to 5394)	500 (353 to 708)	167 (120 to 233)

Genotype I (pre-vaccination)	55.2 (36 to 84.6)	55.3 (35.3 to 86.7)	5 (5 to 5)	5 (5 to 5)
Genotype I (post-vaccination)	1016 (703 to 1467)	1988 (1427 to 2770)	170 (130 to 223)	155 (117 to 206)
Genotype II (pre-vaccination)	46.5 (31.9 to 67.9)	34.2 (22.7 to 51.4)	5 (5 to 5)	5 (5 to 5)
Genotype II (post-vaccination)	921 (625 to 1356)	1566 (1090 to 2250)	157 (119 to 206)	121 (93.7 to 156)
Genotype III (pre-vaccination)	39.2 (27 to 57)	40.6 (25.7 to 64)	5 (5 to 5)	5 (5 to 5)
Genotype III (post-vaccination)	1107 (726 to 1689)	2089 (1405 to 3105)	189 (140 to 255)	98.2 (73.2 to 132)
Genotype IV (pre-vaccination)	25.2 (18.1 to 35.1)	20 (13.8 to 28.9)	5 (5 to 5)	5 (5 to 5)
Genotype IV (post-vaccination)	604 (387 to 944)	829 (575 to 1195)	25.3 (19.1 to 33.5)	17 (13.6 to 21.3)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Persistence of Seroprotection to JE-CV Antigens Up To Five Years Following Vaccination

End point title	Summary of Persistence of Seroprotection to JE-CV Antigens Up To Five Years Following Vaccination
End point description:	
Japanese Encephalitis virus neutralizing antibody measurement was assessed by the PRNT50 assay.	
End point type	Other pre-specified
End point timeframe:	
Day 0 (pre-vaccination) up to 5 years after final vaccination	

End point values	JE-CV/Hepatitis A (Group 1)	Hepatitis A/JE-CV (Group 2)	JE-CV/Hepatitis A (Group 3)	Hepatitis A/JE-CV (Group 4)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	50	101	99
Units: Number of subjects				
number (not applicable)				
Homologous virus (pre-vaccination)	45	41	15	2
Homologous virus (post-vaccination)	49	50	98	89
Homologous virus (post-6 months)	48	49	91	80
Homologous virus (post-1 year)	46	44	81	71
Homologous virus (post-2 years)	41	41	74	64
Homologous virus (post-3 years)	40	38	66	52
Homologous virus (post-4 years)	41	36	63	54
Homologous virus (post-5 years)	40	38	55	44
Genotype I (pre-vaccination)	40	41	8	3
Genotype I (post-vaccination)	49	50	95	93
Genotype I (post-6 months)	47	48	95	86
Genotype II (pre-vaccination)	39	39	9	2
Genotype II (post-vaccination)	49	50	93	93

Genotype II (post-6 months)	47	48	90	80
Genotype III (pre-vaccination)	41	38	5	1
Genotype III (post-vaccination)	49	50	96	92
Genotype III (post-6 months)	48	48	73	62
Genotype IV (pre-vaccination)	39	32	5	0
Genotype IV (post-vaccination)	48	50	73	65
Genotype IV (post-6 months)	47	48	68	46

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Persistence of Neutralizing Antibody Titers to JE-CV Up To Five Years Following Vaccination

End point title	Summary of Persistence of Neutralizing Antibody Titers to JE-CV Up To Five Years Following Vaccination

End point description:

Japanese Encephalitis virus neutralizing antibody measurement was assessed by the PRNT50 assay.

End point type	Other pre-specified

End point timeframe:

Day 0 (pre-vaccination) up to 5 years after final vaccination

End point values	JE-CV/Hepatitis A (Group 1)	Hepatitis A/JE-CV (Group 2)	JE-CV/Hepatitis A (Group 3)	Hepatitis A/JE-CV (Group 4)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	50	101	99
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Homologous virus (pre-vaccination)	48.6 (33.5 to 70.4)	41.1 (27.2 to 62.2)	6.11 (5.51 to 6.78)	5.15 (4.94 to 5.37)
Homologous virus (post-vaccination)	1956.7 (1227.1 to 3120)	3722.2 (2489.2 to 5565.9)	517.6 (371.7 to 720.9)	167.1 (120.2 to 232.2)
Homologous virus (post-6 months)	892.1 (566.1 to 1405.8)	1244.3 (798.8 to 1938.3)	96.6 (71.4 to 130.9)	49.8 (36.8 to 67.4)
Homologous virus (post-1 year)	339 (216 to 531)	621 (382 to 1009)	78.8 (57.8 to 107)	49 (34.9 to 68.6)
Homologous virus (post-2 years)	414 (246 to 698)	662 (403 to 1088)	94.2 (66 to 134)	67.1 (46.3 to 97.3)
Homologous virus (post-3 years)	422 (273 to 654)	505 (339 to 751)	146 (102 to 208)	90.5 (62.6 to 131)
Homologous virus (post-4 years)	360 (223 to 582)	559 (306 to 1023)	137 (100 to 188)	110 (77.5 to 157)
Homologous virus (post-5 years)	222 (151 to 328)	287 (183 to 449)	68.8 (48.3 to 98.1)	58.2 (36.4 to 93)
Genotype I (pre-vaccination)	54.8 (36.1 to 83.3)	55.3 (35.2 to 86.9)	5.62 (5.18 to 6.11)	5.18 (4.96 to 5.41)
Genotype I (post-vaccination)	1015.8 (703.4 to 1466.9)	2116.7 (1519.8 to 2948.1)	186.8 (142.2 to 245.3)	163.1 (122.5 to 217.1)

Genotype I (post-6 months)	863.5 (573.9 to 1299.3)	981 (678.4 to 1418.4)	81.4 (62.8 to 105.5)	52.4 (40.2 to 68.2)
Genotype II (pre-vaccination)	46.5 (31.9 to 67.9)	33.3 (22.3 to 49.6)	5.75 (5.16 to 6.4)	5.2 (4.9 to 5.53)
Genotype II (post-vaccination)	920.6 (624.9 to 1356.2)	1763.4 (1199.3 to 2592.9)	163.2 (125.5 to 212.3)	126.8 (97.8 to 164.4)
Genotype II (post-6 months)	581.2 (402.9 to 838.3)	714.4 (520.4 to 980.7)	72.3 (54.4 to 96.1)	42.4 (31.7 to 56.8)
Genotype III (pre-vaccination)	37.6 (25.8 to 54.7)	41.1 (26.5 to 63.7)	5.39 (5.04 to 5.76)	5.08 (4.93 to 5.23)
Genotype III (post-vaccination)	1107.1 (725.8 to 1688.7)	2210.4 (1498.2 to 3261)	200.2 (151.5 to 264.6)	102.1 (75.8 to 137.6)
Genotype III (post-6 months)	513.1 (326.5 to 806.5)	645.7 (438.7 to 950.4)	31.1 (23.3 to 41.5)	20.2 (15.6 to 26.3)
Genotype IV (pre-vaccination)	25.2 (18.1 to 35.1)	19.7 (13.8 to 28.2)	5.31 (5.03 to 5.6)	5 (5 to 5)
Genotype IV (post-vaccination)	604 (386.6 to 943.6)	874 (610 to 1252.3)	28.5 (21.5 to 37.7)	18.1 (14.3 to 23)
Genotype IV (post-6 months)	279.4 (194.1 to 402.3)	363.4 (256.8 to 514.3)	21 (16.2 to 27.2)	12.6 (9.93 to 16)

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 Day 28 post-vaccination.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10

Reporting groups	
Reporting group title	JE-CV/Hepatitis A (Group 1)
Reporting group description:	
Children aged 2 to 5 years of age received one dose of Japanese Encephalitis ChimeriVax™ (JE-CV) as first vaccination and one dose of Hepatitis A as second vaccination 28 days apart.	
Reporting group title	Hepatitis A/JE-CV (Group 2)
Reporting group description:	
Children aged 2 to 5 years of age received one dose of Hepatitis A as first vaccination and one dose of JE-CV as second vaccination 28 days apart.	
Reporting group title	JE-CV/Hepatitis A (Group 3)
Reporting group description:	
Toddlers aged 12 to 24 months of age received one dose of JE-CV as first vaccination and one dose of Hepatitis A as second vaccination 28 days apart.	
Reporting group title	Hepatitis A/JE-CV (Group 4)
Reporting group description:	
Toddlers aged 12 to 24 months of age received one dose of Hepatitis A as first vaccination and one dose of JE-CV as second vaccination 28 days apart.	

Serious adverse events	JE-CV/Hepatitis A (Group 1)	Hepatitis A/JE-CV (Group 2)	JE-CV/Hepatitis A (Group 3)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 50 (6.00%)	3 / 51 (5.88%)	11 / 101 (10.89%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed[1]	0 / 50 (0.00%)	1 / 50 (2.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed[2]	0 / 50 (0.00%)	1 / 50 (2.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Bronchiolitis			
subjects affected / exposed[3]	0 / 50 (0.00%)	0 / 50 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed[4]	1 / 50 (2.00%)	0 / 50 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed[5]	0 / 50 (0.00%)	1 / 50 (2.00%)	4 / 101 (3.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed[6]	1 / 50 (2.00%)	0 / 50 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpangina			
subjects affected / exposed[7]	0 / 50 (0.00%)	0 / 50 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed[8]	0 / 50 (0.00%)	0 / 50 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed[9]	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed[10]	0 / 50 (0.00%)	1 / 50 (2.00%)	2 / 101 (1.98%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			

subjects affected / exposed[11]	1 / 50 (2.00%)	0 / 50 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed[12]	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed[13]	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Hepatitis A/JE-CV (Group 4)		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 99 (10.10%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed[1]	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed[2]	3 / 99 (3.03%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchiolitis			
subjects affected / exposed[3]	2 / 99 (2.02%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchitis			

subjects affected / exposed[4]	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed[5]	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis rotavirus				
subjects affected / exposed[6]	1 / 99 (1.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpangina				
subjects affected / exposed[7]	1 / 99 (1.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed[8]	1 / 99 (1.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed[9]	1 / 99 (1.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed[10]	1 / 99 (1.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia viral				
subjects affected / exposed[11]	1 / 99 (1.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				

subjects affected / exposed[12]	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed[13]	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: 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 to this adverse event. These numbers are expected to be equal.
Justification: 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 to this adverse event. These numbers are expected to be equal.
Justification: 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 to this adverse event. These numbers are expected to be equal.
Justification: 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 to this adverse event. These numbers are expected to be equal.
Justification: 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 to this adverse event. These numbers are expected to be equal.
Justification: 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 to this adverse event. These numbers are expected to be equal.
Justification: 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 to this adverse event. These numbers are expected to be equal.
Justification: 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 to this adverse event. These numbers are expected to be equal.
Justification: 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 to this adverse event. These numbers are expected to be equal.
Justification: 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 to this adverse event. These numbers are expected to be equal.
Justification: 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 to this adverse event. These numbers are expected to be equal.
Justification: 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 to this adverse event. These numbers are expected to be equal.
Justification: 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.

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

Non-serious adverse events	JE-CV/Hepatitis A (Group 1)	Hepatitis A/JE-CV (Group 2)	JE-CV/Hepatitis A (Group 3)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 50 (30.00%)	18 / 51 (35.29%)	43 / 101 (42.57%)
Nervous system disorders			
Drowsiness			
alternative assessment type: Systematic			
subjects affected / exposed[14]	0 / 50 (0.00%)	0 / 51 (0.00%)	22 / 101 (21.78%)
occurrences (all)	0	0	22
Headache			
alternative assessment type: Systematic			
subjects affected / exposed[15]	7 / 48 (14.58%)	14 / 51 (27.45%)	0 / 101 (0.00%)
occurrences (all)	7	14	0
General disorders and administration site conditions			
Fever			
alternative assessment type: Systematic			
subjects affected / exposed[16]	8 / 50 (16.00%)	14 / 51 (27.45%)	23 / 100 (23.00%)
occurrences (all)	8	14	23
Injection site Erythema			
alternative assessment type: Systematic			
subjects affected / exposed[17]	8 / 48 (16.67%)	9 / 50 (18.00%)	23 / 100 (23.00%)
occurrences (all)	8	9	23
Injection site Pain			
alternative assessment type: Systematic			
subjects affected / exposed[18]	15 / 48 (31.25%)	13 / 50 (26.00%)	0 / 101 (0.00%)
occurrences (all)	15	13	0
Injection site Swelling			
alternative assessment type: Systematic			
subjects affected / exposed[19]	8 / 48 (16.67%)	5 / 50 (10.00%)	6 / 100 (6.00%)
occurrences (all)	8	5	6
Injection site Tenderness			
alternative assessment type: Systematic			

subjects affected / exposed[20]	0 / 50 (0.00%)	0 / 51 (0.00%)	43 / 101 (42.57%)
occurrences (all)	0	0	43
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	15 / 50 (30.00%)	18 / 51 (35.29%)	0 / 101 (0.00%)
occurrences (all)	15	18	0
Pyrexia			
subjects affected / exposed[21]	3 / 50 (6.00%)	0 / 50 (0.00%)	0 / 101 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal disorders			
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed[22]	0 / 50 (0.00%)	0 / 51 (0.00%)	23 / 100 (23.00%)
occurrences (all)	0	0	23
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed[23]	4 / 50 (8.00%)	1 / 50 (2.00%)	0 / 101 (0.00%)
occurrences (all)	4	1	0
Rhinorrhoea			
subjects affected / exposed[24]	3 / 50 (6.00%)	1 / 50 (2.00%)	13 / 101 (12.87%)
occurrences (all)	3	1	16
Skin and subcutaneous tissue disorders			
Heat rash			
subjects affected / exposed[25]	3 / 48 (6.25%)	0 / 51 (0.00%)	0 / 101 (0.00%)
occurrences (all)	4	0	0
Psychiatric disorders			
Crying abnormal			
alternative assessment type: Systematic			
subjects affected / exposed[26]	0 / 50 (0.00%)	0 / 51 (0.00%)	24 / 101 (23.76%)
occurrences (all)	0	0	24
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed[27]	0 / 50 (0.00%)	0 / 51 (0.00%)	32 / 101 (31.68%)
occurrences (all)	0	0	32
Musculoskeletal and connective tissue disorders			

Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	14 / 50 (28.00%)	10 / 51 (19.61%)	0 / 101 (0.00%)
occurrences (all)	14	10	0
Infections and infestations			
Bronchitis			
subjects affected / exposed[28]	3 / 48 (6.25%)	3 / 50 (6.00%)	0 / 101 (0.00%)
occurrences (all)	3	3	0
Nasopharyngitis			
subjects affected / exposed[29]	1 / 50 (2.00%)	5 / 50 (10.00%)	5 / 101 (4.95%)
occurrences (all)	1	5	5
Upper respiratory tract infection			
subjects affected / exposed	8 / 50 (16.00%)	8 / 51 (15.69%)	35 / 101 (34.65%)
occurrences (all)	9	8	35
Metabolism and nutrition disorders			
Appetite lost			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	28 / 101 (27.72%)
occurrences (all)	0	0	28

Non-serious adverse events	Hepatitis A/JE-CV (Group 4)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 99 (35.35%)		
Nervous system disorders			
Drowsiness			
alternative assessment type: Systematic			
subjects affected / exposed[14]	14 / 98 (14.29%)		
occurrences (all)	14		
Headache			
alternative assessment type: Systematic			
subjects affected / exposed[15]	0 / 99 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fever			
alternative assessment type: Systematic			

subjects affected / exposed[16]	28 / 98 (28.57%)		
occurrences (all)	28		
Injection site Erythema			
alternative assessment type: Systematic			
subjects affected / exposed[17]	22 / 98 (22.45%)		
occurrences (all)	22		
Injection site Pain			
alternative assessment type: Systematic			
subjects affected / exposed[18]	0 / 99 (0.00%)		
occurrences (all)	0		
Injection site Swelling			
alternative assessment type: Systematic			
subjects affected / exposed[19]	11 / 98 (11.22%)		
occurrences (all)	11		
Injection site Tenderness			
alternative assessment type: Systematic			
subjects affected / exposed[20]	20 / 98 (20.41%)		
occurrences (all)	20		
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed[21]	0 / 99 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed[22]	21 / 99 (21.21%)		
occurrences (all)	21		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed[23]	0 / 99 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			

subjects affected / exposed[24]	11 / 99 (11.11%)		
occurrences (all)	12		
Skin and subcutaneous tissue disorders			
Heat rash			
subjects affected / exposed[25]	0 / 99 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Crying abnormal			
alternative assessment type: Systematic			
subjects affected / exposed[26]	21 / 98 (21.43%)		
occurrences (all)	21		
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed[27]	24 / 98 (24.49%)		
occurrences (all)	24		
Musculoskeletal and connective tissue disorders			
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed[28]	0 / 99 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed[29]	11 / 99 (11.11%)		
occurrences (all)	12		
Upper respiratory tract infection			
subjects affected / exposed	35 / 99 (35.35%)		
occurrences (all)	39		
Metabolism and nutrition disorders			
Appetite lost			
alternative assessment type: Systematic			
subjects affected / exposed	32 / 99 (32.32%)		
occurrences (all)	32		

Notes:
[14] - 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 vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[15] - 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 vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[16] - 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 vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[17] - 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 vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[18] - 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 vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[19] - 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 vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[20] - 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 vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[21] - 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: 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.
[22] - 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 vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[23] - 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: 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.
[24] - 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: 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.
[25] - 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: 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.
[26] - 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 vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[27] - 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 vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[28] - 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: 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.
[29] - 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: The total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2007	Exclusion criteria were revised such that children were allowed to receive oral polio vaccine in the 4 weeks preceding the first trial vaccination and hepatitis B serology was defined as hepatitis B surface antigen; results of study H-040-009 were updated as blind was opened: presentation of SAEs per vaccine group, and seroconversion rates given per vaccine group.
30 November 2007	Inclusion and exclusion criteria defining groups 1 and 2 were corrected to enlarge the JE primary vaccination period; a precision on the safety intensity scales were included (Mild -> Grade 1; Moderate -> Grade 2; Severe -> Grade 3).
10 January 2008	Clarification of the reconstitution procedure for the investigational product; change in the Sponsor representatives of the Safety Review Committee.
07 April 2008	Modification of assay methods for determination of flavivirus status at baseline (dengue and JE status were to be assessed by PRNT50 assays instead of ELISA); a first screening was performed by dengue ELISA and then only positive samples were to be further analyzed by dengue PRNT50; JE PRNT50 was performed on all samples as part of baseline immunogenicity assessment.
21 August 2008	Addition of a 5-year follow-up to evaluate yearly persistence of immune response to JE after one dose of JE-CV; addition of an observational objective for the characterization of JE-CV viruses by measurement of viral plaque size and RNA sequencing; adjustment of titer defining seroconversion from 20 (1/dil) to 10 (1/dil) for wild-type virus strains.
30 October 2008	Revision of the definition of the Per Protocol population; definition for the Other Immunogenicity set was added.
04 June 2009	Clarification of SAE reporting was updated such that any related SAEs occurring between the 6-month follow-up visit and the end of the study were reported to the Sponsor by the Investigator.
11 December 2009	Change in the exclusion criteria such that subjects were allowed to participate in another clinical trial from the second year of follow-up period onward.
11 December 2010	Extension of the time window for the coming yearly visits to +/- 60 days instead of +/- 30 days to facilitate the participation of yearly visits and to anticipate any unexpected circumstances.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported