Clinical trial results:
A Phase III, Multicenter, Observer-blind, Safety and Immunogenicity Study of Rabies Vaccine and Japanese Encephalitis Vaccine Administered Concomitantly and/or Separately According to 1 of 2 Different Pre-exposure Prophylaxis Schedules to Healthy Adult Subjects

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2011-005173-23
Trial protocol	AT
Global end of trial date	28 October 2013

Results information

Result version number	v2 (current)
This version publication date	11 June 2016
First version publication date	28 December 2014
Version creation reason	• Correction of full data set re-QC of the study needed because of EudraCT system glitch and updates are required.

Trial information

Trial identification

Sponsor protocol code	V49_23

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01662440
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics SRL
Sponsor organisation address	Via Fiorentina 1 , Siena, Italy, 53100
Public contact	Posting Director, Novartis Vaccines and Diagnostics SRL, RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director , Novartis Vaccines and Diagnostics SRL, RegistryContactVaccinesUS@novartis.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 September 2014
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of Rabies and JE vaccines given concomitantly or alone and according to either of 2 schedules for pre-exposure prophylaxis

Immunogenicity:
Primary:
1. To establish non-inferiority of the immune response of Rabies vaccine (administered concomitantly with JE vaccine) accelerated schedule as compared to Rabies vaccine administered alone following the conventional schedule.
2. To establish non-inferiority of the immune response of JE vaccine (administered concomitantly with Rabies vaccine), accelerated schedule as compared to JE vaccine administered alone following the conventional schedule.

Protection of trial subjects:

This trial was performed with the ethical principles that have their origin in the Declaration of Helsinki that are consistent with GCP according to International
Conference on Harmonization (ICH) guidelines, the applicable regulatory requirements(s) for the country in which the study is conducted, and applicable standard operating procedures (SOPs). Specifically, this trial was based on adequately performed laboratory and animal experimentation; it was conducted under a protocol reviewed and approved by the EC and by scientifically and medically qualified persons; the benefits of the study were in proportion to the risks; the rights and welfare of the subjects were respected; the physicians conducting the trial did not find the hazards to outweigh the potential benefits; each subject, or where applicable, each subject's legally acceptable representative(s) gave his or her written informed consent before any protocol-driven tests or evaluations were performed. A copy of the ICH GCP guidelines and the Declaration of Helsinki were included in the investigator's study file.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 August 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Scientific research
Long term follow-up duration	10 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 100
Country: Number of subjects enrolled	Germany: 479
Country: Number of subjects enrolled	Switzerland: 82

Worldwide total number of subjects	661
EEA total number of subjects	579

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	654
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from five sites in Germany, one site in Austria, and one site in Switzerland.

Pre-assignment

Screening details:

All subjects were included in the trial.

Period 1

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

Blinding implementation details:

Subjects were not informed which injections were active and which were placebo. All vaccines were assembled away from the view of the subject and blinded site staff members. All injections were administered by a designated unblinded staff member who was not involved in the evaluation of safety or in immunogenicity analyses. All other site personnel remained blinded to study vaccine group. Laboratory personnel determining antibody titers were not aware of vaccine group assignments.

Arms

Are arms mutually exclusive?	Yes
Arm title	R/JE – Conv

Arm description:

Subjects received Rabies (R) and Japanese Encephalitis (JE) vaccines, conventional schedule, ie, Rabies vaccination on days 1, 8, and 29, and placebo on day 4 in the right arm or leg; and JE vaccination on day 1 and 29, and placebo on day 8 in the left arm.

Arm type	Active comparator
Investigational medicinal product name	Rabies, whole virus vaccine (inactivated, Germany)
Investigational medicinal product code	SUB25746
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received three injections (days 1, 8, and 29) of 1 mL.

Investigational medicinal product name	Japanese encephalitis vaccine (inactivated, adsorbed)
Investigational medicinal product code	SUB30399
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received two injections (days 1 and 29) of 0.5 mL.

Arm title	R/JE – Acc

Arm description:

Subjects received Rabies and JE vaccines, accelerated schedule, ie, Rabies vaccination on days 1, 4, and 8, and placebo on day 29 in the right arm or leg; and JE vaccination on days 1 and 8, and placebo on day 29 in the left arm.

Arm type	Experimental

Investigational medicinal product name	Rabies, whole virus vaccine (inactivated, Germany)
Investigational medicinal product code	SUB25746
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received three injections (days 1, 4, and 8) of 1 mL containing ≥ 2.5 IU of antigen.

Investigational medicinal product name	Japanese encephalitis vaccine (inactivated, adsorbed)
Investigational medicinal product code	SUB30399
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received two injections (days 1 and 8) of 0.5 mL containing 6 µg of antigen.

Arm title	R – Conv

Arm description:

Subjects received Rabies vaccine, conventional schedule, ie, Rabies vaccination on days 1, 8, and 29, and placebo on day 4 in the right arm or leg; and placebo on days 1, 8 and 29 in the left arm.

Arm type	Active comparator
Investigational medicinal product name	Rabies, whole virus vaccine (inactivated, Germany)
Investigational medicinal product code	SUB25746
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received three injections (days 1, 8, and 29) of 1 mL.

Arm title	JE – Conv

Arm description:

Subjects received JE vaccine, conventional schedule, ie, placebo on days 1, 4, 8 and 29 in the right arm or leg; and JE vaccination on days 1 and 29 and placebo injection on day 8 in the left arm.

Arm type	Active comparator
Investigational medicinal product name	Japanese encephalitis vaccine (inactivated, adsorbed)
Investigational medicinal product code	SUB30399
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received two injections (days 1 and 29) of 0.5 mL.

Number of subjects in period 1	R/JE – Conv	R/JE – Acc	R – Conv
Started	167	217	221
Completed	158	211	215
Not completed	9	6	6
Consent withdrawn by subject	5	2	2
Adverse event, non-fatal	1	-	-

Subject moved to another country	-	1	-
Death	-	1	-
Lost to follow-up	2	2	4
Protocol deviation	1	-	-

Number of subjects in period 1	JE – Conv
Started	56
Completed	52
Not completed	4
Consent withdrawn by subject	2
Adverse event, non-fatal	1
Subject moved to another country	-
Death	-
Lost to follow-up	1
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	R/JE – Conv

Reporting group description:

Subjects received Rabies (R) and Japanese Encephalitis (JE) vaccines, conventional schedule, ie, Rabies vaccination on days 1, 8, and 29, and placebo on day 4 in the right arm or leg; and JE vaccination on day 1 and 29, and placebo on day 8 in the left arm.

Reporting group title	R/JE – Acc

Reporting group description:

Subjects received Rabies and JE vaccines, accelerated schedule, ie, Rabies vaccination on days 1, 4, and 8, and placebo on day 29 in the right arm or leg; and JE vaccination on days 1 and 8, and placebo on day 29 in the left arm.

Reporting group title	R – Conv

Reporting group description:

Subjects received Rabies vaccine, conventional schedule, ie, Rabies vaccination on days 1, 8, and 29, and placebo on day 4 in the right arm or leg; and placebo on days 1, 8 and 29 in the left arm.

Reporting group title	JE – Conv

Reporting group description:

Subjects received JE vaccine, conventional schedule, ie, placebo on days 1, 4, 8 and 29 in the right arm or leg; and JE vaccination on days 1 and 29 and placebo injection on day 8 in the left arm.

Reporting group values	R/JE – Conv	R/JE – Acc	R – Conv
Number of subjects	167	217	221
Age categorical			
Units: Subjects			
Age continuous			
Analysis was done on the All Enrolled Set, ie, all subjects who have signed an informed consent, undergone screening procedure(s) and were randomized.			
Units: years			
arithmetic mean	37.3	36.8	35.7
standard deviation	± 13.4	± 12.7	± 12.6
Gender categorical			
Analysis was done on the all enrolled set, ie, all subjects who have signed an informed consent, undergone screening procedure(s) and were randomized.			
Units: Subjects			
Female	76	128	125
Male	91	89	96

Reporting group values	JE – Conv	Total	
Number of subjects	56	661	
Age categorical			
Units: Subjects			
Age continuous			
Analysis was done on the All Enrolled Set, ie, all subjects who have signed an informed consent, undergone screening procedure(s) and were randomized.			

Units: years			
arithmetic mean	38.8		
standard deviation	± 13.3	-	

Gender categorical			
Analysis was done on the all enrolled set, ie, all subjects who have signed an informed consent, undergone screening procedure(s) and were randomized.			
Units: Subjects			
Female	30	359	
Male	26	302	

End points

End points reporting groups

Reporting group title	R/JE – Conv

Reporting group description:

Subjects received Rabies (R) and Japanese Encephalitis (JE) vaccines, conventional schedule, ie, Rabies vaccination on days 1, 8, and 29, and placebo on day 4 in the right arm or leg; and JE vaccination on day 1 and 29, and placebo on day 8 in the left arm.

Reporting group title	R/JE – Acc

Reporting group description:

Subjects received Rabies and JE vaccines, accelerated schedule, ie, Rabies vaccination on days 1, 4, and 8, and placebo on day 29 in the right arm or leg; and JE vaccination on days 1 and 8, and placebo on day 29 in the left arm.

Reporting group title	R – Conv

Reporting group description:

Subjects received Rabies vaccine, conventional schedule, ie, Rabies vaccination on days 1, 8, and 29, and placebo on day 4 in the right arm or leg; and placebo on days 1, 8 and 29 in the left arm.

Reporting group title	JE – Conv

Reporting group description:

Subjects received JE vaccine, conventional schedule, ie, placebo on days 1, 4, 8 and 29 in the right arm or leg; and JE vaccination on days 1 and 29 and placebo injection on day 8 in the left arm.

Primary: 1) Percentages of Subjects With RVNA Concentrations ≥0.5 IU/mL At 7 Days After Last Active Vaccination

End point title	1) Percentages of Subjects With RVNA Concentrations ≥0.5 IU/mL At 7 Days After Last Active Vaccination[1]

End point description:

Immune response was measured as the percentage of subjects with rabies virus neutralizing antibody (RVNA) concentrations ≥0.5 IU/mL, evaluated using the rapid fluorescent focus inhibition test, before vaccination (day 1) and 7 days after last active vaccination, i.e. the third out of four vaccinations given in the accelerated Rabies vaccine schedule and the fourth out of four vaccinations given in the conventional Rabies vaccine schedule.
As per study design, this primary immunogenicity outcome measure aimed to demonstrate non-inferiority of R/JE - Acc Vs R - Conv.
Analysis was done on the per-protocol (PP) dataset, ie, the subjects who received the vaccine correctly, provided evaluable serum samples at the relevant time points, and had no major protocol violations as defined prior to unblinding.

End point type	Primary

End point timeframe:

Day 7 after last active vaccination (day 15 – group received accelerated schedule, day 36 – group received conventional schedule)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Acc	R – Conv		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	207		
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 7 after last active vaccination	100 (97 to 100)	100 (97 to 100)		

Statistical analyses

Statistical analysis title	non-inferiority of the immune response

Statistical analysis description:

To establish non-inferiority of the immune response of Rabies vaccine (administered concomitantly with JE vaccine) accelerated schedule as compared to Rabies vaccine administered alone following the conventional schedule at 7 days after last active vaccination.

Comparison groups	R/JE – Acc v R – Conv
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Method	Miettinen and Nurminen
Parameter estimate	Difference in percentages of subjects
Point estimate	0
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-2.8
upper limit	2.8

Notes:

[2] - The immune response of accelerated schedule of the Rabies vaccine considered non-inferior to the conventional schedule if the lower bound of the two-sided 97.5% Confidence Intervals (CI) of the difference in the percentages of subjects with RVNA titer ≥0.5 IU/mL measured 7 days after last active vaccination is greater than -5.

Primary: 2) Percentages of Subjects With PRNT50 Titer ≥1:10 At 28 Days After Last Active Vaccination

End point title	2) Percentages of Subjects With PRNT50 Titer ≥1:10 At 28 Days After Last Active Vaccination[3]

End point description:

Immune response was measured as the percentages of subjects with a titer of ≥1:10 in a 50% plaque reduction neutralization test (PRNT50) 28 days after last active vaccination, ie, the second out of three vaccinations given in the accelerated JE vaccine schedule and the third out of three vaccinations given in the conventional JE vaccine schedule.
As per study design, this primary immunogenicity outcome measure aimed to demonstrate non-inferiority of R/JE - Acc Vs JE - Conv.

End point type	Primary

End point timeframe:

Day 28 after last active vaccination (day 36 – group received accelerated schedule, day 57 – group received conventional schedule)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Acc	JE – Conv		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	49		
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 28 after last active vaccination	99 (96 to 100)	100 (93 to 100)		

Statistical analyses

Statistical analysis title	Non-inferiority of the immune response

Statistical analysis description:

Non-inferiority of the immune response of JE vaccine (administered concomitantly with Rabies vaccine) accelerated schedule as compared to JE vaccine administered alone following the conventional schedule at 28 day after last active vaccination

Comparison groups	R/JE – Acc v JE – Conv
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Method	Miettinen and Nurminen
Parameter estimate	Difference in percentages of subjects
Point estimate	-1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-4.8
upper limit	7.9

Notes:

[4] - The immune response of accelerated schedule of the JE vaccine is considered non-inferior to the conventional schedule if the lower bound of the two-sided 97.5% CI of the difference in the percentages of subjects with PRNT50 titer ≥1:10 measured 28 days after last active vaccination is greater than -10.

Secondary: 3) RVNA Geometric Mean Concentrations (GMCs) At 28Days After Last Active Vaccination

End point title	3) RVNA Geometric Mean Concentrations (GMCs) At 28Days After Last Active Vaccination[5]

End point description:

Immune response was measured as the RVNA GMCs), 28 days after last active vaccination, i.e. day 57 for all groups that received the conventional schedule.
Data were adjusted using ANOVA model, as per protocol specification.
Analysis was done on the PP dataset.

End point type	Secondary

End point timeframe:

28 days after last active vaccination (day 57)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Conv	R – Conv		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	204		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Day 28 after last active vaccination	11 (9 to 12)	9.9 (8.57 to 11)		

Statistical analyses

Statistical analysis title	Non-inferiority of the immune response

Statistical analysis description:

Non-inferiority of the immune response of Rabies vaccine (administered concomitantly with JE vaccine) as compared to Rabies vaccines (administered alone) as given according to conventional schedule at 28day after last active vaccination

Comparison groups	R – Conv v R/JE – Conv
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Between groups ratio of GMCs]
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.32

Notes:

[6] - The conventional schedule of Rabies vaccine co-administered with JE vaccine considered non inferior to the conventional schedule of Rabies vaccine administered alone if the lower bound of the two-sided 95% CI of the ratio of GMCs measured 28 days after last active vaccination is greater than 0.667.

Secondary: 4) PRNT50 GMTs At 28 Days After Last Active Vaccination

End point title	4) PRNT50 GMTs At 28 Days After Last Active Vaccination[7]

End point description:

Immune response was measured as the PRNT50 GMTs 28 days after last active vaccination, ie, day 57 for all groups that received the conventional schedule.
Data were adjusted using ANOVA model, as per protocol specifications.
Analysis was done on the PP dataset.

End point type	Secondary

End point timeframe:

28 days after last active vaccination (day 57)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Conv	JE – Conv		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	49		
Units: Titers				
geometric mean (confidence interval 95%)				
Day 28 after last active vaccination	291 (256 to 331)	331 (265 to 415)		

Statistical analyses

Statistical analysis title	Non-inferiority of the immune response

Statistical analysis description:

Non-inferiority of the immune response of JE vaccine (administered concomitantly with Rabies vaccine) as compared to JE vaccine (administered alone) as given according to conventional schedule at day 28 after last active vaccination.

Comparison groups	R/JE – Conv v JE – Conv
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	Ratio of GMTs
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.13

Notes:

[8] - The conventional schedule of JE vaccine co-administered with Rabies vaccine considered non inferior to the conventional schedule of JE vaccine administered alone if the lower bound of the two-sided 95% CI of the ratio of GMTs measured 28 days after last active vaccination is greater than 0.5.

Secondary: 5) Percentages of Subjects With RVNA Concentrations ≥0.5 IU/mL At 28Days After Last Active Vaccination

End point title	5) Percentages of Subjects With RVNA Concentrations ≥0.5 IU/mL At 28Days After Last Active Vaccination[9]

End point description:

Immune response was measured as the percentage of subjects with RVNA concentrations ≥0.5 IU/mL, 28 days after last active vaccination, i.e. day 36 for the group that received the accelerated schedule and day 57 for the group that received the conventional schedule.
As per study design, this secondary immunogenicity outcome measure aimed to demonstrate non-inferiority of R/JE - Acc Vs R - Conv.
Analysis was done on the PP set.

End point type	Secondary

End point timeframe:

Day 36 and day 57 (28 days after last active vaccination)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Acc	R – Conv		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	204		
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 28 after last active vaccination	99 (96 to 100)	100 (97 to 100)		

Statistical analyses

Statistical analysis title	Non-inferiority of the Rabies immune response

Statistical analysis description:

Non-inferiority of the Rabies immune response (administered concomitantly with JE vaccine) as given according to an accelerated schedule as compared Rabies vaccine (administered alone) as given to a conventional schedule at day 28 after last active vaccination.

Comparison groups	R/JE – Acc v R – Conv
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	Difference in percentages of subjects
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	1.4

Notes:

[10] - The immune response of accelerated schedule of the Rabies vaccine is considered non-inferior to the Rabies vaccine conventional schedule if the lower bound of the two-sided 95% CI of the difference in the percentages of subjects with RVNA concentrations ≥0.5 IU/mL measured 28 days after last active vaccine administration is greater than -5.

Secondary: 6) Percentage of Subjects With PRNT50 Titer ≥1:10 At 7 Days After Last Active Vaccination

End point title	6) Percentage of Subjects With PRNT50 Titer ≥1:10 At 7 Days After Last Active Vaccination[11]

End point description:

Immune response was measured as the percentage of subjects with PRNT50 titer of ≥1:10, 7 days after last active vaccination, ie, day 15 for the group that received the accelerated schedule and day 36 for the group that received the conventional schedule.
As per study design, this secondary immunogenicity outcome measure aimed to demonstrate non-inferiority of R/JE - Acc Vs JE - Conv.
Analysis was done on the PP dataset.

End point type	Secondary

End point timeframe:

Day 15 and day 36 (28 after last active vaccination)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Acc	JE – Conv		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	47		
Units: Percentage of subjects				
number (confidence interval 95%)				
Day 7 after last active vaccination	99 (96 to 100)	100 (92 to 100)		

Statistical analyses

Statistical analysis title	Non-inferiority of the immune response

Statistical analysis description:

Non-inferiority of the immune response of JE vaccine (administered concomitantly with Rabies vaccine) as given according to an accelerated schedule as compared to JE vaccine (administered alone) as given according to a conventional schedule at 7day after last active vaccine administration.

Comparison groups	R/JE – Acc v JE – Conv
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
Parameter estimate	Difference in percentages of subjects
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	6.2

Notes:

[12] - The immune response of accelerated schedule of the JE vaccine considered non-inferior to the conventional schedule if the lower bound of the two-sided 95% CI of the difference in the percentages of subjects with PRNT50 titer ≥1:10 measured 7 days after last active vaccine administration is greater than -10.

Secondary: 7) Kinetics of Rabies Immune Response Measured as Percentage of Subjects With RVNA Concentrations ≥0.5 IU/mL

End point title	7) Kinetics of Rabies Immune Response Measured as Percentage of Subjects With RVNA Concentrations ≥0.5 IU/mL[13]

End point description:

To evaluate the kinetics of antibody response to Rabies vaccine, the immunogenicity was measured as the percentage of subjects with RVNA concentrations ≥0.5 IU/mL on days 1, 8, 15, 36, 57, 91, 181, and 366.

End point type	Secondary

End point timeframe:

Day 1, 15, 36, 57, 91, 181 and Day 366

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Conv	R/JE – Acc	R – Conv	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166	215	218	
Units: Percentage of Subjects				
number (confidence interval 95%)				
Day 1	1 (0.015 to 3)	1 (0 to 3)	1 (0 to 4)	
Day 8 (N=161, 210, 213)	4 (2 to 9)	16 (11 to 21)	4 (2 to 8)	
Day 15 (N=161, 209, 210)	99 (96 to 100)	100 (97 to 100)	99 (97 to 100)	
Day 36 (N=157, 206, 207)	100 (98 to 100)	99 (96 to 100)	100 (97 to 100)	
Day 57 (157, 204, 204)	100 (98 to 100)	97 (93 to 99)	100 (97 to 100)	
Day 91 (N=152, 206, 204)	99 (95 to 100)	85 (79 to 90)	98 (95 to 99)	
Day 181 (N= 155, 200, 202)	88 (82 to 92)	75 (68 to 81)	89 (84 to 93)	
Day 366 (154, 199, 204)	76 (68 to 82)	68 (61 to 74)	80 (74 to 85)	

Statistical analyses

No statistical analyses for this end point

Secondary: 8) Kinetics of Rabies Immune Response Measured as the RVNA GMCs

End point title	8) Kinetics of Rabies Immune Response Measured as the RVNA GMCs[14]

End point description:

To evaluate the kinetics of antibody response to Rabies vaccine, the immunogenicity was measured as the RVNA GMCs on days 1, 8, 15, 36, 57, 91, 181, and 366.
Analysis was done on the PP dataset.

End point type	Secondary

End point timeframe:

Day 1, 8, 15, 36, 57, 91, 181, and 366

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Conv	R/JE – Acc	R – Conv	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166	215	218	
Units: IU/mL				
geometric mean (confidence interval 95%)				
Day 1	0.052 (0.048 to 0.056)	0.053 (0.049 to 0.056)	0.054 (0.05 to 0.057)	
Day 8 (N=161, 210, 213)	0.071 (0.061 to 0.084)	0.13 (0.12 to 0.16)	0.076 (0.066 to 0.088)	
Day 15 (N=161, 209, 210)	21 (17 to 25)	26 (22 to 30)	24 (20 to 28)	
Day 36 (N=157, 206, 207)	14 (12 to 17)	5.75 (4.95 to 6.67)	13 (11 to 15)	
Day 57 (N=157, 204, 204)	10 (8.72 to 12)	3.01 (2.59 to 3.51)	9.66 (8.31 to 11)	

Day 91 (N=152, 206, 204)	4.79 (3.98 to 5.76)	1.63 (1.39 to 1.91)	5.04 (4.29 to 5.91)	
Day 181 (N= 155, 200, 202)	1.86 (1.51 to 2.3)	1 (0.83 to 1.21)	2.04 (1.69 to 2.46)	
Day 366 (N=154, 199, 204)	0.93 (0.75 to 1.16)	0.82 (0.67 to 1)	1.14 (0.94 to 1.38)	

Statistical analyses

No statistical analyses for this end point

Secondary: 9) Kinetics of JE Immune Response Measured as Percentages of Subjects With PRNT50 ≥1:10 IU/mL

End point title	9) Kinetics of JE Immune Response Measured as Percentages of Subjects With PRNT50 ≥1:10 IU/mL[15]

End point description:

To evaluate the kinetics of antibody response to JE vaccine, the immunogenicity was measured as the percentages of subjects with PRNT50 titer ≥1:10 on days 1, 36, 57, 181, and 366 (group that received JE vaccine as a conventional schedule).

Analysis was done on the PP dataset.

End point type	Secondary

End point timeframe:

Days 1, 36, 57, 181 and 366

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Conv	JE – Conv		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	55		
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 1	1 (0 to 4)	9 (3 to 20)		
Day 36 (157, 47)	99 (97 to 100)	100 (92 to 100)		
Day 57 (N=157, 49)	100 (98 to 100)	100 (93 to 100)		
Day 181 (N=155, 49)	94 (88 to 97)	92 (80 to 98)		
Day 366 (N=154, 48)	86 (79 to 91)	88 (75 to 95)		

Statistical analyses

No statistical analyses for this end point

Secondary: 10) Kinetics of JE Immune Response Measured as Percentage of Subjects With PRNT50 Titers ≥1:10

End point title	10) Kinetics of JE Immune Response Measured as Percentage of Subjects With PRNT50 Titers ≥1:10[16]

End point description:

To evaluate the kinetics of antibody response to JE vaccine, the immunogenicity was measured as the percentage of subjects with PRNT50 titer ≥1:10 on days 1, 15, 22, 36, 57, 91, 181, and 366 (group that received JE vaccine as an accelerated schedule).
Analysis was done on the PP dataset.

End point type	Secondary

End point timeframe:

Day 1, 15, 22, 36, 57, 91, 181, and 366

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Acc			
Subject group type	Reporting group			
Number of subjects analysed	215			
Units: Percentage of Subjects				
geometric mean (confidence interval 95%)				
Day 1	6 (3 to 10)			
Day 15 (N= 209)	99 (96 to 100)			
Day 22 (N= 208)	100 (97 to 100)			
Day 36 (N= 206)	99 (96 to 100)			
Day 57 (N= 204)	98 (95 to 100)			
Day 91 (N= 206)	98 (95 to 99)			
Day 181 (N= 200)	98 (94 to 99)			
Day 366 (N= 199)	94 (90 to 97)			

Statistical analyses

No statistical analyses for this end point

Secondary: 11) Kinetics of JE Immune Response Measured as PRNT50 GMTs

End point title	11) Kinetics of JE Immune Response Measured as PRNT50 GMTs[17]

End point description:

To evaluate the kinetics of antibody response to JE vaccine, the immunogenicity was measured as the PRNT50 GMTs on days 1, 36, 57, 181, and 366 (groups that received JE vaccine as a conventional schedule).
Analysis was done on the PP dataset.

End point type	Secondary

End point timeframe:

day 1, 36, 57, 181, and 366

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Conv	JE – Conv		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	55		
Units: Titers				
geometric mean (confidence interval 95%)				
Day 1	5.13 (4.84 to 5.43)	5.73 (5.2 to 6.33)		
Day 36 (N=157, 47)	292 (247 to 346)	376 (277 to 510)		
Day 57 (N= 157, 49)	299 (254 to 352)	337 (252 to 451)		
Day 181 (N=155, 49)	63 (53 to 75)	64 (47 to 87)		
Day 366 (N=154, 48)	39 (33 to 47)	39 (28 to 54)		

Statistical analyses

No statistical analyses for this end point

Secondary: 12) Kinetics of JE Immune Response Measured as PRNT50 GMTs

End point title	12) Kinetics of JE Immune Response Measured as PRNT50 GMTs[18]

End point description:

To evaluate the kinetics of antibody response to JE vaccine, the immunogenicity was measured as the PRNT50 GMTs on days 1, 15, 22, 36, 57, 91, 181, and 366 (group that received JE vaccine as an accelerated schedule).
Analysis was done on the PP dataset.

End point type	Secondary

End point timeframe:

Day 1, 15, 22, 36, 57, 91, 181, and 366

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Acc			
Subject group type	Reporting group			
Number of subjects analysed	215			
Units: Titers				
geometric mean (confidence interval 95%)				
Day 1	5.63 (5.35 to 5.92)			
Day 15 (N= 209)	715 (608 to 842)			
Day 22 (N= 208)	1255 (1068 to 1475)			
Day 36 (N= 206)	690 (595 to 801)			
Day 57 (N= 204)	372 (322 to 430)			
Day 91 (N= 206)	228 (192 to 272)			

Day 181 (N= 200) Day 366 (N= 199)	151 (130 to 176) 117 (100 to 137)			

Statistical analyses

No statistical analyses for this end point

Secondary: 13) Number of Subjects Who Reported Solicited Local Adverse Events After Each Rabies Vaccination, conventional schedule

End point title	13) Number of Subjects Who Reported Solicited Local Adverse Events After Each Rabies Vaccination, conventional schedule[19]

End point description:

Safety was assessed as the number of subjects who reported solicited local adverse events (AEs) after each rabies vaccination given according to the conventional schedule as follows: from day 1 through day 7 (vaccination on day 1), day 8 through day 14 (vaccination on day 8), or day 29 through day 35 (vaccination on day 29).
Analysis was done on the solicited safety set, i.e. the subjects in the exposed population who provided postvaccination solicited safety data.

End point type	Secondary

End point timeframe:

Day 1 through day 7 after each vaccination (day 1, 8 and 29)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Conv	R – Conv		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	220		
Units: Number of Subjects				
Erythema (day 1 to 7)	13	28		
Induration (day 1 to 7)	3	11		
Pain (day 1 to 7)	43	72		
Erythema (day 8 to 14)	8	29		
Induration (day 8 to 14)	10	17		
Pain (day 8 to 14)	57	90		
Erythema (day 29 to 35)	23	45		
Induration (day 29 to 35)	18	32		
Pain (day 29 to 35)	52	87		

Statistical analyses

No statistical analyses for this end point

Secondary: 14) Number of Subjects Who Reported Solicited Local Adverse Events After Each Rabies Vaccination, accelerated schedule

End point title	14) Number of Subjects Who Reported Solicited Local Adverse

	Events After Each Rabies Vaccination, accelerated schedule[20]

End point description:

Safety was assessed as the number of subjects who reported solicited local adverse events (AEs) after each rabies vaccination given according to accelerated schedule as follows: from day 1 through day 7 (vaccination on day 1), day 4 through day 10 (vaccination on day 4), day 8 through day 14 (vaccination on day 8).
Analysis was done on the solicited safety set.

End point type	Secondary

End point timeframe:

Day 1 through day 7 after each vaccination (on day 1, 4, 8 and 29)

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Acc			
Subject group type	Reporting group			
Number of subjects analysed	217			
Units: Number of Subjects				
Erythema (day 1 to 7)	31			
Induration (day 1 to 7)	16			
Pain (day 1 to 7)	69			
Erythema (day 4 to 10)	17			
Induration (day 4 to 10)	9			
Pain (day 4 to 10)	55			
Erythema (day 8 to 14)	31			
Induration (day 8 to 14)	15			
Pain (day 8 to 14)	87			

Statistical analyses

No statistical analyses for this end point

Secondary: 15) Number of Subjects Who Reported Solicited Local AEs After Each JE Vaccination, conventional schedule

End point title	15) Number of Subjects Who Reported Solicited Local AEs After Each JE Vaccination, conventional schedule[21]

End point description:

Safety was assessed as the number of subjects who reported solicited local AEs after each JE vaccination given according to conventional schedule as follow: from day 1 through day 7 (vaccination on day 1) and day 29 through day 35 (vaccination on day 29).
Analysis was done on the solicited safety set.

End point type	Secondary

End point timeframe:

Day 1 through day 7 after each vaccination (on day 1 and 29)

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Conv	JE – Conv		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	56		
Units: Number of Subjects				
Erythema (day 1 to 7)	20	6		
Induration (day 1 to 7)	13	5		
Pain (day 1 to 7)	82	26		
Erythema (day 29 to 35)	12	5		
Induration (day 29 to 35)	5	4		
Pain (day 29 to 35)	46	12		

Statistical analyses

No statistical analyses for this end point

Secondary: 16) Number of Subjects Who Reported Solicited Local AEs After Each JE Vaccination, accelerated schedule

End point title	16) Number of Subjects Who Reported Solicited Local AEs After Each JE Vaccination, accelerated schedule[22]

End point description:

Safety was assessed as the number of subjects who reported solicited local AEs after each JE vaccination given according to accelerated or conventional schedule as follow: from day 1 through day 7 (vaccination on day 1), day 8 through day 14 (vaccination on day 8).
Analysis was done on the solicited safety set.

End point type	Secondary

End point timeframe:

Day 1 through day 7 after each vaccination (on day 1 and 8)

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Acc			
Subject group type	Reporting group			
Number of subjects analysed	217			
Units: Number of Subjects				
Erythema (day 1 to 7)	30			
Induration (day 1 to 7)	19			
Pain (day 1 to 7)	102			
Erythema (day 8 to 14)	18			
Induration (day 8 to 14)	12			
Pain (day 8 to 14)	60			

Statistical analyses

No statistical analyses for this end point

Secondary: 17) Number of Subjects in the R/JE – Conv group Who Reported Solicited Local AEs After Each Placebo Injection

End point title	17) Number of Subjects in the R/JE – Conv group Who Reported Solicited Local AEs After Each Placebo Injection[23]

End point description:

Safety was assessed as the number of subjects in the R/JE – Conv group who reported solicited local AEs after each placebo injection given according to conventional schedule as follow: from day 4 through day 10 (injection on day 4) and day 8 through day 14 (injection on day 8).
Analysis was done on the solicited safety set.

End point type	Secondary

End point timeframe:

Day 1 through day 7 after each injection (day 4 and 8)

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Conv			
Subject group type	Reporting group			
Number of subjects analysed	166			
Units: Number of Subjects				
Erythema (day 4 to 10)	8			
Induration (day 4 to 10)	1			
Pain (day 4 to 10)	7			
Erythema (day 8 to 14)	1			
Induration (day 8 to 14)	0			
Pain (day 8 to 14)	19			

Statistical analyses

No statistical analyses for this end point

Secondary: 18) Number of Subjects in the R/JE – Accccelerated schedule group Who Reported Solicited Local AEs After Each Placebo Injection

End point title	18) Number of Subjects in the R/JE – Accccelerated schedule group Who Reported Solicited Local AEs After Each Placebo Injection[24]

End point description:

Safety was assessed as the number of subjects who reported solicited local AEs after each placebo injection given according to accelerated schedule as follow: from day 29 through day 35 (injection on day 29).
Analysis was done on the solicited safety set.

End point type	Secondary

End point timeframe:

Day 1 through day 7 after each injection (day 1, 4, 8 and 29)

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R/JE – Acc			
Subject group type	Reporting group			
Number of subjects analysed	213			
Units: Number of Subjects				
Erythema (day 29 to 35)	15			
Erythema (day 29 to 35 after 2nd Placebo dose)	14			
Induration (day 29 to 35)	6			
Induration (day 29 to 35 after 2nd Placebo dose)	4			
Pain (day 29 to 35)	15			
Pain (day 29 to 35 after 2nd Placebo dose)	19			

Statistical analyses

No statistical analyses for this end point

Secondary: 19) Number of Subjects in the R – Conventional schedule group Who Reported Solicited Local AEs After Each Placebo Injection

End point title	19) Number of Subjects in the R – Conventional schedule group Who Reported Solicited Local AEs After Each Placebo Injection[25]

End point description:

Safety was assessed as the number of subjects in the R – Conventional schedule group who reported solicited local AEs after each placebo injection given according to conventional schedule as follow: from day 1 through day 7 (injection on day 1), day 4 through day 10 (injection on day 4), day 8 through day 14 (injection on day 8), and day 29 through day 35 (injection on day 29).
Analysis was done on the solicited safety set.

End point type	Secondary

End point timeframe:

Day 1 through day 7 after each injection (day 1, 4, 8 and 29)

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	R – Conv			
Subject group type	Reporting group			
Number of subjects analysed	220			
Units: Number of Subjects				
Erythema (day 1 to 7)	20			
Induration (day 1 to 7)	4			
Pain (day 1 to 7)	26			
Erythema (day 4 to 10)	13			
Induration (day 4 to 10)	4			
Pain (day 4 to 10)	15			
Erythema (day 8 to 14)	11			
Induration (day 8 to 14)	5			
Pain (day 8 to 14)	20			
Erythema (day 29 to 35)	15			

Induration (day 29 to 35)	4			
Pain (day 29 to 35)	28			

Statistical analyses

No statistical analyses for this end point

Secondary: 20) Number of Subjects in the JE – Conventional schedule group Who Reported Solicited Local AEs After Each Placebo Injection

End point title	20) Number of Subjects in the JE – Conventional schedule group Who Reported Solicited Local AEs After Each Placebo Injection[26]

End point description:

Safety was assessed as the number of subjects in the JE – Conventional schedule group who reported solicited local AEs after each placebo injection given according to conventional schedule as follow: from day 1 through day 7 (injection on day 1), day 4 through day 10 (injection on day 4), day 8 through day 14 (injection on day 8), and day 29 through day 35 (injection on day 29).
Analysis was done on the solicited safety set.

End point type	Secondary

End point timeframe:

Day 1 through day 7 after each injection (day 1, 4, 8 and 29)

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis done for this endpoint.

End point values	JE – Conv			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Number of Subjects				
Erythema (day 1 to 7)	3			
Induration (day 1 to 7)	5			
Pain (day 1 to 7)	7			
Erythema (day 4 to 10)	3			
Induration (day 4 to 10)	2			
Pain (day 4 to 10)	3			
Erythema (day 8 to 14)	4			
Erythema (day 8 to 14 after 2nd Placebo dose)	3			
Induration (day 8 to 14)	1			
Induration (day 8 to 14 after 2nd Placebo dose)	1			
Pain (day 8 to 14)	3			
Pain (day 8 to 14 after 2nd Placebo dose)	5			
Erythema (day 29 to 35)	3			
Induration (day 29 to 35)	1			
Pain (day 29 to 35)	3			

Statistical analyses

No statistical analyses for this end point

Secondary: 21) Number of Subjects Who Reported Solicited Systemic AEs and Other Indicators of Reactogenicity After Each Vaccination

End point title	21) Number of Subjects Who Reported Solicited Systemic AEs and Other Indicators of Reactogenicity After Each Vaccination

End point description:

Safety was assessed as the number of subjects who reported solicited systemic AEs and other indicators of reactogenicity after each vaccination given according to accelerated and conventional schedule. Analysis was done on the solicited safety set.

End point type	Secondary

End point timeframe:

Day 1 through day 7 after each vaccination (day 1, 4, 8 and 29)

End point values	R/JE – Conv	R/JE – Acc	R – Conv	JE – Conv
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	166	217	220	56
Units: Number of Subjects				
Fatigue (day 1 to 7)	39	56	46	16
Headache (day 1 to 7)	35	46	38	14
Myalgia (day 1 to 7)	27	55	31	7
Arthralgia (day 1 to 7)	8	13	7	1
Loss of Appetite (day1 to day 7)	10	8	12	6
Nausea (day1 to day 7)	8	7	13	4
Body temperature (≥38 °C, day 1 to day 7)	1	2	2	0
Analgesic/Antipyretic used (day 1 to day 7)	11	11	8	3
Fatigue (day 4 to 10)	14	30	33	5
Headache (day 4 to 10)	17	28	29	3
Myalgia (day 4 to 10)	11	19	14	1
Arthralgia (day 4 to 10)	1	9	9	0
Loss of Appetite (day4 to day 10)	4	8	9	2
Nausea (day4 to day 10)	4	5	8	0
Body temperature (≥38 °C, day 4 to day 10)	1	1	2	0
Analgesic/Antipyretic used (day 4 to 10)	8	10	15	2
Fatigue (day 8 to 14)	24	47	47	6
Headache (day 8 to 14)	33	43	41	3
Myalgia (day 8 to 14)	22	41	38	1
Arthralgia (day 8 to 14)	6	9	13	1
Loss of Appetite (day8 to day 14)	10	14	13	2

Nausea (day8 to day 14)	5	14	16	2
Body temperature (≥38 °C, day 8 to 14)	2	1	5	0
Analgesic/Antipyretic used (day 8 to 14)	10	17	20	2
Fatigue (day 29 to 35)	21	29	36	3
Headache (day 29 to 35)	27	22	40	4
Myalgia (day 29 to 35)	23	15	28	2
Arthralgia (day 29 to 35)	5	6	14	1
Body temperature (≥38 °C, day 29 to day 35)	1	2	1	0
Analgesic/Antipyretic used (day 29 to day 35)	9	10	11	3
Loss if appetite (day 29 to day 25)	2	8	9	2
nausea (day29 to day 25)	7	12	9	2

Statistical analyses

No statistical analyses for this end point

Secondary: 22) Numbers of Subjects Reporting Unsolicited AEs After Any Vaccination From Day 1 Through Day 57

End point title	22) Numbers of Subjects Reporting Unsolicited AEs After Any Vaccination From Day 1 Through Day 57

End point description:

Safety was assessed as the number of subjects who reported unsolicited AEs after any vaccination given according to accelerated and conventional schedule.

End point type	Secondary

End point timeframe:

Day 1 through Day 57

End point values	R/JE – Conv	R/JE – Acc	R – Conv	JE – Conv
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	166	217	220	56
Units: Numbers of Subjects				
Any AE	69	108	110	29
SAE	2	3	2	3
AEs leading to premature withdrawal	1	0	0	1

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited AEs were collected for 7 days after each vaccination. All unsolicited AEs, serious adverse events (SAEs), AEs leading to study and/or treatment withdrawal were collected through day 57. From day 57 to day 366 vaccine-related SAEs were collected.

Adverse event reporting additional description:

Solicited adverse events were collected by systematic assessment, unsolicited AEs by non-systematic assessment. SAEs analysis was done one the unsolicited safety set, other AEs analysis was done on the overall safety set.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	R/JE – Conv

Reporting group description:

Subjects received Rabies (R) and Japanese Encephalitis (JE) vaccines, conventional schedule, ie, Rabies vaccination on days 1, 8, and 29, and placebo on day 4 in the right arm or leg; and JE vaccination on day 1 and 29, and placebo on day 8 in the left arm.

Reporting group title	R – Conv

Reporting group description:

Subjects received Rabies vaccine, conventional schedule, ie, Rabies vaccination on days 1, 8, and 29, and placebo on day 4 in the right arm or leg; and placebo on days 1, 8 and 29 in the left arm.

Reporting group title	JE – Conv

Reporting group description:

Subjects received JE vaccine, conventional schedule, ie, placebo on days 1, 4, 8 and 29 in the right arm or leg; and JE vaccination on days 1 and 29 and placebo injection on day 8 in the left arm.

Reporting group title	R/JE – Acc

Reporting group description:

Subjects received Rabies and JE vaccines, accelerated schedule, ie, Rabies vaccination on days 1, 4, and 8, and placebo on day 29 in the right arm or leg; and JE vaccination on days 1 and 8, and placebo on day 29 in the left arm.

Serious adverse events	R/JE – Conv	R – Conv	JE – Conv
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 166 (1.20%)	2 / 220 (0.91%)	3 / 56 (5.36%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian germ cell teratoma benign			
subjects affected / exposed	0 / 166 (0.00%)	0 / 220 (0.00%)	0 / 56 (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
Injury, poisoning and procedural			

complications			
Humerus fracture			
subjects affected / exposed	1 / 166 (0.60%)	0 / 220 (0.00%)	0 / 56 (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
Meniscus injury			
subjects affected / exposed	0 / 166 (0.00%)	0 / 220 (0.00%)	0 / 56 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 166 (0.00%)	1 / 220 (0.45%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 220 (0.45%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 166 (0.00%)	1 / 220 (0.45%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eyelid oedema			
subjects affected / exposed	0 / 166 (0.00%)	0 / 220 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 166 (0.00%)	0 / 220 (0.00%)	0 / 56 (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
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	0 / 166 (0.00%)	0 / 220 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 220 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pruritus generalised			
subjects affected / exposed	0 / 166 (0.00%)	0 / 220 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 166 (0.00%)	0 / 220 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	1 / 166 (0.60%)	0 / 220 (0.00%)	0 / 56 (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

Serious adverse events	R/JE – Acc		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 217 (1.38%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian germ cell teratoma benign			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Humerus fracture			

subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meniscus injury			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Eyelid oedema			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Pruritus generalised			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	R/JE – Conv	R – Conv	JE – Conv
Total subjects affected by non-serious adverse events			
subjects affected / exposed	138 / 166 (83.13%)	185 / 220 (84.09%)	45 / 56 (80.36%)
Nervous system disorders			
Headache			
subjects affected / exposed	63 / 166 (37.95%)	95 / 220 (43.18%)	19 / 56 (33.93%)
occurrences (all)	139	189	30
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	54 / 166 (32.53%)	84 / 220 (38.18%)	19 / 56 (33.93%)
occurrences (all)	107	189	33

Injection site erythema			
subjects affected / exposed	48 / 166 (28.92%)	85 / 220 (38.64%)	13 / 56 (23.21%)
occurrences (all)	90	163	28
Injection site induration			
subjects affected / exposed	29 / 166 (17.47%)	48 / 220 (21.82%)	10 / 56 (17.86%)
occurrences (all)	54	77	19
Injection site pain			
subjects affected / exposed	115 / 166 (69.28%)	131 / 220 (59.55%)	31 / 56 (55.36%)
occurrences (all)	314	342	62
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	19 / 166 (11.45%)	35 / 220 (15.91%)	9 / 56 (16.07%)
occurrences (all)	29	52	10
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 166 (7.83%)	31 / 220 (14.09%)	3 / 56 (5.36%)
occurrences (all)	21	48	3
Myalgia			
subjects affected / exposed	50 / 166 (30.12%)	60 / 220 (27.27%)	10 / 56 (17.86%)
occurrences (all)	86	115	13
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	22 / 166 (13.25%)	32 / 220 (14.55%)	7 / 56 (12.50%)
occurrences (all)	25	36	7
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	19 / 166 (11.45%)	27 / 220 (12.27%)	9 / 56 (16.07%)
occurrences (all)	31	50	12

Non-serious adverse events	R/JE – Acc		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	186 / 217 (85.71%)		
Nervous system disorders			
Headache			
subjects affected / exposed	94 / 217 (43.32%)		
occurrences (all)	185		
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	93 / 217 (42.86%) 182		
Injection site erythema subjects affected / exposed occurrences (all)	73 / 217 (33.64%) 160		
Injection site induration subjects affected / exposed occurrences (all)	43 / 217 (19.82%) 81		
Injection site pain subjects affected / exposed occurrences (all)	146 / 217 (67.28%) 418		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	31 / 217 (14.29%) 44		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	29 / 217 (13.36%) 37		
Myalgia subjects affected / exposed occurrences (all)	75 / 217 (34.56%) 137		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	33 / 217 (15.21%) 37		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	24 / 217 (11.06%) 43		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 April 2012	Protocol Number V49_23, Version 2.0, Amendment 1 – Date: 06 APR 12, (revised from Version 1.0, Date: 05 DEC 11)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported