Clinical trial results:
A Phase 3, Open-label, Multicenter Study to Evaluate Long-term Immunogenicity and Boostability of Immune Responses in Adults who Received Different Primary Vaccination Regimens of Pre-exposure Prophylaxis with Purified Chick-Embryo Cell Rabies Vaccine Administered Concomitantly or Separately from a Japanese Encephalitis Vaccine

Summary

EudraCT number	2015-000382-31
Trial protocol	DE AT
Global end of trial date	15 March 2023

Results information

Result version number	v1 (current)
This version publication date	06 January 2024
First version publication date	06 January 2024

Trial information

Trial identification

Sponsor protocol code	205214

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02545517
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium, B-1330
Public contact	GSK Response Center, GlaxoSmithKline, 44 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 44 8664357343, GSKClinicalSupportHD@gsk.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	24 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 December 2022
Global end of trial reached?	Yes
Global end of trial date	15 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is an extension study aimed:

• To evaluate the safety of a booster dose of PCEC rabies vaccine following a primary series of accelerated or conventional rabies PrEP IM regimen in the parent study (V49_23).

• To compare the long-term (up to approx.10 years) persistence of antibody responses (i.e. time until antibody concentrations drop below 0.5 IU/mL) in participants who received a primary series of accelerated or conventional rabies PrEP intramuscular (IM) regimen in the parent study (V49_23).

• To evaluate the antibody responses to a booster dose of PCEC rabies vaccine administered to participants with RVNA concentrations <0.5 IU/mL following a primary series of accelerated or conventional rabies PrEP IM regimen in the parent study (V49_23).

Protection of trial subjects:

Study participants receiving a booster vaccination were observed at the site for at least 30 minutes after immunization for any immediate reactions. Appropriate medical treatment was readily available during the observation period.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 October 2015
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	Austria: 67
Country: Number of subjects enrolled	Germany: 327
Country: Number of subjects enrolled	Switzerland: 65
Worldwide total number of subjects	459
EEA total number of subjects	394

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)	451
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Up to 459 participants, who successfully completed rabies pre-exposure prophylaxis (PrEP) regimens in parent study (V49_23) (NCT01662440, EudraCT ID- 2011-005173-23) and did not have protocol deviations which could impact the immunogenicity response (e.g., wrong vaccination) were enrolled in this extension study.

Pre-assignment

Screening details:

As prespecified in protocol, Visit 1 in the extension study corresponds to Year 3, i.e. approximately 3 years after completion of rabies primary series in the parent study. Subsequent visits (2,3,4,5,6,7 and 8) occurred at yearly intervals applied after completion of parent study (Year 4, 5, 6, 7, 8, 9 and 10).

Period 1

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

Arms

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

Arm description:

Participants who completed the Rabies PrEP regimen on days 1, 8 and 29, and Japanese Encephalitis (JE) primary series regimen on days 1 and 29 in the parent study (V49_23) and who received at least one booster dose of purified chick embryo cell culture (PCEC) rabies vaccine in this extension study, if Rabies Virus Neutralizing Antibody (RNVA) concentrations were less than (<)0.5 IU/mL at scheduled visits.

Arm type	Experimental
Investigational medicinal product name	Purified chick-embryo cell derived (PCEC) rabies vaccine
Investigational medicinal product code	
Other name	Rabipur
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Intramuscular use

Dosage and administration details:

A single dose of 1.0 mL of the PCEC rabies vaccine was administered intramuscularly in the deltoid of the non-dominant arm for participants with RVNA concentrations <0.5 IU/mL.

Arm title	Acc-R/JE Group

Arm description:

Participants who completed the Rabies PrEP regimen on days 1, 4 and 8 and JE primary series regimen on days 1 and 8 in the parent study (V49_23) and who received at least one booster dose of PCEC rabies vaccine in this extension study, if RNVA concentrations were <0.5 IU/mL at scheduled visits.

Arm type	Experimental
Investigational medicinal product name	PCEC rabies vaccine
Investigational medicinal product code	
Other name	Rabipur
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Intramuscular use

Dosage and administration details:

A single dose of 1.0 mL of the PCEC rabies vaccine was administered intramuscularly in the deltoid of the non-dominant arm for participants with RVNA concentrations <0.5 IU/mL.

Arm title	Conv-R Group

Arm description:

Participants who completed the Rabies PrEP regimen on days 1, 8 and 29 in the parent study (V49_23) and who received at least one booster dose of PCEC rabies vaccine in this extension study, if RNVA concentrations were <0.5 IU/mL at scheduled visits.

Arm type	Experimental
Investigational medicinal product name	PCEC rabies vaccine
Investigational medicinal product code	
Other name	Rabipur
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Intramuscular use

Dosage and administration details:

A single dose of 1.0 mL of the PCEC rabies vaccine was administered intramuscularly in the deltoid of the non-dominant arm for participants with RVNA concentrations <0.5 IU/mL.

Number of subjects in period 1	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group
Started	126	157	176
Completed	98	123	135
Not completed	28	34	41
Adverse event, serious fatal	2	2	1
Consent withdrawn by subject	5	8	9
Unspecified	2	4	3
Lost to follow-up	14	13	17
Administrative reason	5	6	10
Protocol deviation	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Conv-R/JE Group
Reporting group description:	
Participants who completed the Rabies PrEP regimen on days 1, 8 and 29, and Japanese Encephalitis (JE) primary series regimen on days 1 and 29 in the parent study (V49_23) and who received at least one booster dose of purified chick embryo cell culture (PCEC) rabies vaccine in this extension study, if Rabies Virus Neutralizing Antibody (RNVA) concentrations were less than (<)0.5 IU/mL at scheduled visits.	
Reporting group title	Acc-R/JE Group
Reporting group description:	
Participants who completed the Rabies PrEP regimen on days 1, 4 and 8 and JE primary series regimen on days 1 and 8 in the parent study (V49_23) and who received at least one booster dose of PCEC rabies vaccine in this extension study, if RNVA concentrations were <0.5 IU/mL at scheduled visits.	
Reporting group title	Conv-R Group
Reporting group description:	
Participants who completed the Rabies PrEP regimen on days 1, 8 and 29 in the parent study (V49_23) and who received at least one booster dose of PCEC rabies vaccine in this extension study, if RNVA concentrations were <0.5 IU/mL at scheduled visits.	

Reporting group values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group
Number of subjects	126	157	176
Age categorical Units: Participants			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	122	155	174
From 65-84 years	4	2	2
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	37.9	38.7	36.6
standard deviation	± 13.2	± 13.0	± 12.8
Sex: Female, Male Units: Participants			
Male	65	63	75
Female	61	94	101
Race/Ethnicity, Customized Units: Subjects			
ASIAN	1	0	1
BLACK OR AFRICAN AMERICAN	0	2	0
OTHER UNSPECIFIED	0	1	2
WHITE	125	154	173

Reporting group values	Total		

Number of subjects	459		
Age categorical Units: Participants			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	451		
From 65-84 years	8		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Male	203		
Female	256		
Race/Ethnicity, Customized Units: Subjects			
ASIAN	2		
BLACK OR AFRICAN AMERICAN	2		
OTHER UNSPECIFIED	3		
WHITE	452		

End points

End points reporting groups

Reporting group title	Conv-R/JE Group
Reporting group description:	
Participants who completed the Rabies PrEP regimen on days 1, 8 and 29, and Japanese Encephalitis (JE) primary series regimen on days 1 and 29 in the parent study (V49_23) and who received at least one booster dose of purified chick embryo cell culture (PCEC) rabies vaccine in this extension study, if Rabies Virus Neutralizing Antibody (RNVA) concentrations were less than (<)0.5 IU/mL at scheduled visits.	
Reporting group title	Acc-R/JE Group
Reporting group description:	
Participants who completed the Rabies PrEP regimen on days 1, 4 and 8 and JE primary series regimen on days 1 and 8 in the parent study (V49_23) and who received at least one booster dose of PCEC rabies vaccine in this extension study, if RNVA concentrations were <0.5 IU/mL at scheduled visits.	
Reporting group title	Conv-R Group
Reporting group description:	
Participants who completed the Rabies PrEP regimen on days 1, 8 and 29 in the parent study (V49_23) and who received at least one booster dose of PCEC rabies vaccine in this extension study, if RNVA concentrations were <0.5 IU/mL at scheduled visits.	

Primary: Number of participants reporting serious adverse events (SAEs) after a booster dose of purified chick embryo cell culture (PCEC) rabies vaccine

End point title	Number of participants reporting serious adverse events (SAEs) after a booster dose of purified chick embryo cell culture (PCEC) rabies vaccine[1]
End point description:	
A SAE is defined as any untoward medical occurrence that at any dose results in one or more of the following: death, is life-threatening, required/prolonged hospitalization, persistent or significant disability/incapacity, congenital anomaly/or birth defect, an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the participants or may require intervention to prevent one of the other outcomes listed. Safety is assessed as the number of participants reporting SAEs after a booster dose of PCEC rabies vaccine administered in this extension study, if RNVA concentrations were <0.5 IU/mL, following a primary series of accelerated or conventional rabies pre-exposure (PrEP) intramuscular (IM) regimen in the parent study. The analysis was performed on the Safety Set which included all enrolled participants who received a booster dose and reported safety data.	
End point type	Primary
End point timeframe:	
From booster vaccination [6 to 9 months after Year 3 (3 years after primary series of vaccination)] up until completion of the safety follow-up period (10 years after primary series of 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).	

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	47	53	
Units: Participants	2	0	3	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who had their RNVA concentrations drop below 0.5 IU/mL between Year 3 and Year 4

End point title	Number of participants who had their RNVA concentrations drop below 0.5 IU/mL between Year 3 and Year 4[2]

End point description:

The analysis was performed on the FAS-2: long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

Year 3 to Year 4 (after primary series of vaccination)

Notes:

[2] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	93	92	133	
Units: Participants	5	5	7	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who had their Rabies Virus Neutralizing Antibody (RNVA) concentrations drop below 0.5 international units (IU) per milliliter (mL) between Day 366 and Year 3

End point title	Number of participants who had their Rabies Virus Neutralizing Antibody (RNVA) concentrations drop below 0.5 international units (IU) per milliliter (mL) between Day 366 and Year 3[3]

End point description:

The analysis was performed on the Full Analysis Set-2 (FAS-2): long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

Day 366 to Year 3 (after primary series of vaccination)

Notes:

[3] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	96	98	133	
Units: Participants	1	1	2	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who had their RNVA concentrations drop below 0.5 IU/mL between Year 4 and Year 5

End point title	Number of participants who had their RNVA concentrations drop below 0.5 IU/mL between Year 4 and Year 5[4]

End point description:

The analysis was performed on the FAS-2: long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

Year 4 to Year 5 (after primary series of vaccination)

Notes:

[4] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	84	117	
Units: Participants	7	0	4	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who had their RNVA concentrations drop below 0.5 IU/mL between Year 9 and Year 10

End point title	Number of participants who had their RNVA concentrations drop below 0.5 IU/mL between Year 9 and Year 10[5]

End point description:

The analysis was performed on the FAS-2: long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

Year 9 to Year 10 (after primary series of vaccination)

Notes:

[5] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	69	85	
Units: Participants	2	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who had their RNVA concentrations drop below 0.5 IU/mL between Year 8 and Year 9

End point title	Number of participants who had their RNVA concentrations drop below 0.5 IU/mL between Year 8 and Year 9[6]

End point description:

The analysis was performed on the FAS-2: long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

Year 8 to Year 9 (after primary series of 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66	72	93	
Units: Participants	1	0	2	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who had their RNVA concentrations drop below 0.5 IU/mL between Year 5 and Year 6

End point title	Number of participants who had their RNVA concentrations drop below 0.5 IU/mL between Year 5 and Year 6[7]

End point description:

The analysis was performed on the FAS-2: long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

Year 5 to Year 6 (after primary series of vaccination)

Notes:

[7] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	83	112	
Units: Participants	3	2	10	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who had their RNVA concentrations drop below 0.5 IU/mL between Year 6 and Year 7

End point title	Number of participants who had their RNVA concentrations drop below 0.5 IU/mL between Year 6 and Year 7[8]

End point description:

The analysis was performed on the FAS-2: long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

Year 6 to Year 7 (after primary series of vaccination)

Notes:

[8] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	78	101	
Units: Participants	0	2	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who had their RNVA concentrations drop below 0.5

IU/mL between Year 7 and Year 8

End point title	Number of participants who had their RNVA concentrations drop below 0.5 IU/mL between Year 7 and Year 8[9]

End point description:

The analysis was performed on the FAS-2: long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

Year 7 to Year 8 (after primary series of vaccination)

Notes:

[9] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	74	97	
Units: Participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: RVNA antibody concentrations 7 days after the booster dose

End point title	RVNA antibody concentrations 7 days after the booster dose[10]

End point description:

RVNA antibody concentrations were measured in terms of Geometric Mean Concentrations (GMCs) and expressed in IU/mL.
Analysis was performed on the Full Analysis Set-1 (FAS-1): booster immunogenicity analysis, which included all eligible participants from the V49_23 study enrolled in this extension study, whom received booster dose (booster dose was administered only when participants reached RVNA concentrations <0.5 IU/mL) and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

At Day 7 after booster dose

Notes:

[10] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	46	52	
Units: IU/mL				
geometric mean (confidence interval 95%)	4.2 (2.8 to 6.4)	4.2 (2.8 to 6.2)	4.4 (3.0 to 6.4)	

Statistical analyses

No statistical analyses for this end point

Primary: RVNA Geometric Mean Ratios (GMRs) 7 days after the booster dose versus antibody concentrations before the booster dose

End point title	RVNA Geometric Mean Ratios (GMRs) 7 days after the booster dose versus antibody concentrations before the booster dose[11]

End point description:

GMR was calculated as ratio of post booster dose RVNA GMCs (7-day post booster dose) to the baseline RVNA GMCs (7 days before booster dose).
Analysis was performed on the FAS-1: booster immunogenicity analysis, which included all eligible participants from the V49_23 study enrolled in this extension study, whom received booster dose (booster dose was administered only when participants reached RVNA concentrations <0.5 IU/mL) and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

Day 7 after booster dose compared to baseline (7 days before booster dose)

Notes:

[11] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	46	52	
Units: Ratio				
geometric mean (confidence interval 95%)	23.6 (16.1 to 34.4)	23.4 (16.2 to 33.8)	19.3 (13.7 to 27.3)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with RVNA concentrations greater than or equal to (>=) 0.5 IU/mL, 7 days after booster dose

End point title	Percentage of participants with RVNA concentrations greater than or equal to (>=) 0.5 IU/mL, 7 days after booster dose[12]

End point description:

Analysis was performed on the FAS-1: booster immunogenicity analysis, which included all eligible participants from the V49_23 study enrolled in this extension study, whom received booster dose (booster dose was administered only when participants reached RVNA concentrations <0.5 IU/mL) and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

At Day 7 after booster dose

Notes:

[12] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	46	52	
Units: Percentage of participants				
number (confidence interval 95%)	95.3 (84.2 to 99.4)	89.1 (76.4 to 96.4)	98.1 (89.7 to 100.0)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with RVNA concentrations >= 0.5 IU/mL at Year 6

End point title	Percentage of participants with RVNA concentrations >= 0.5 IU/mL at Year 6[13]

End point description:

The analysis was performed on the FAS-2: long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

At Year 6 after primary series of vaccine administration

Notes:

[13] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	139	158	
Units: Percentage of participants				
number (confidence interval 95%)	60.9 (51.1 to 70.1)	66.2 (57.7 to 74.0)	66.5 (58.5 to 73.8)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with RVNA concentrations >= 0.5 IU/mL at Year 5

End point title	Percentage of participants with RVNA concentrations >= 0.5 IU/mL at Year 5[14]

End point description:

The analysis was performed on the FAS-2: long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

At Year 5 after primary series of vaccine administration

Notes:

[14] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	118	139	160	
Units: Percentage of participants				
number (confidence interval 95%)	66.1 (56.8 to 74.6)	69.1 (60.7 to 76.6)	73.1 (65.6 to 79.8)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with RVNA concentrations >= 0.5 IU/mL at Year 4

End point title	Percentage of participants with RVNA concentrations >= 0.5 IU/mL at Year 4[15]

End point description:

The analysis was performed on the FAS-2: long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

At Year 4 after primary series of vaccine administration

Notes:

[15] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	121	144	166	
Units: Percentage of participants				
number (confidence interval 95%)	74.4 (65.6 to 81.9)	70.8 (62.7 to 78.1)	76.5 (69.3 to 82.7)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with RVNA concentrations >= 0.5 IU/mL at Year 3

End point title	Percentage of participants with RVNA concentrations >= 0.5 IU/mL at Year 3[16]

End point description:

The analysis was performed on the FAS-2: long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

At Year 3 after primary series of vaccine administration

Notes:

[16] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	125	151	172	
Units: Percentage of participants				
number (confidence interval 95%)	81.6 (73.7 to 88.0)	78.8 (71.4 to 85.0)	84.9 (78.6 to 89.9)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with RVNA concentrations >= 0.5 IU/mL at Year 9

End point title	Percentage of participants with RVNA concentrations >= 0.5 IU/mL at Year 9[17]

End point description:

The analysis was performed on the FAS-2: long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

At Year 9 after primary series of vaccine administration

Notes:

[17] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	132	150	
Units: Percentage of participants				
number (confidence interval 95%)	59.3 (49.4 to 68.6)	63.6 (54.8 to 71.8)	64.0 (55.8 to 71.7)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with RVNA concentrations >= 0.5 IU/mL at Year 8

End point title	Percentage of participants with RVNA concentrations >= 0.5 IU/mL at Year 8[18]

End point description:

The analysis was performed on the FAS-2: long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

At Year 8 after primary series of vaccine administration

Notes:

[18] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	107	131	144	
Units: Percentage of participants				
number (confidence interval 95%)	59.8 (49.9 to 69.2)	64.1 (55.3 to 72.3)	64.6 (56.2 to 72.4)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with RVNA concentrations >= 0.5 IU/mL at Year 7

End point title	Percentage of participants with RVNA concentrations >= 0.5 IU/mL at Year 7[19]

End point description:

The analysis was performed on the FAS-2: long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

At Year 7 after primary series of vaccine administration

Notes:

[19] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	135	156	
Units: Percentage of participants				
number (confidence interval 95%)	60.2 (50.3 to 69.5)	64.4 (55.8 to 72.5)	67.3 (59.3 to 74.6)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with RVNA concentrations >= 0.5 IU/mL at Year 10

End point title	Percentage of participants with RVNA concentrations >= 0.5 IU/mL at Year 10[20]

End point description:

The analysis was performed on the FAS-2: long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoint.

End point type	Primary

End point timeframe:

At Year 10 after primary series of vaccine administration

Notes:

[20] - 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: The analysis of this endpoint was descriptive (no statistical hypothesis test was performed).

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	130	142	
Units: Percentage of participants				
number (confidence interval 95%)	56.2 (46.2 to 65.9)	62.3 (53.4 to 70.7)	62.7 (54.2 to 70.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Rabies Virus Neutralizing Antibody concentrations

End point title	Rabies Virus Neutralizing Antibody concentrations

End point description:

Antibody concentrations were measured in terms of GMCs and expressed in IU/mL.
The analysis was performed on the FAS-2: long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoints.

End point type	Secondary

End point timeframe:

At Year 3, Year 4, Year 5, Year 6, Year 7, Year 8, Year 9 and Year 10 after primary series of vaccine administration

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126	157	176	
Units: IU/mL				
geometric mean (confidence interval 95%)				
Year 3	1.21 (0.88 to 1.65)	1.16 (0.87 to 1.55)	1.3 (0.99 to 1.7)	
Year 4	0.69 (0.5 to 0.94)	0.73 (0.55 to 0.97)	0.82 (0.63 to 1.07)	
Year 5	0.66 (0.48 to 0.9)	0.7 (0.53 to 0.94)	0.74 (0.56 to 0.96)	
Year 6	0.5 (0.37 to 0.69)	0.6 (0.45 to 0.8)	0.58 (0.44 to 0.76)	
Year 7	0.49 (0.36 to 0.67)	0.6 (0.45 to 0.79)	0.61 (0.47 to 0.8)	
Year 8	0.56 (0.41 to 0.77)	0.76 (0.57 to 1.01)	0.68 (0.52 to 0.89)	
Year 9	0.53 (0.39 to 0.73)	0.7 (0.53 to 0.94)	0.62 (0.47 to 0.81)	
Year 10	0.59 (0.43 to 0.81)	0.72 (0.54 to 0.96)	0.68 (0.52 to 0.89)	

Statistical analyses

No statistical analyses for this end point

Secondary: Reverse Cumulative percentage for participants with RVNA concentrations >=0.5 IU/mL

End point title	Reverse Cumulative percentage for participants with RVNA concentrations >=0.5 IU/mL

End point description:

As specified in the statistical analysis plan, a graphical presentation of the Reverse Cumulative Distribution Plots for participants with RVNA concentrations >=0.5 IU/mL was analyzed for this outcome measure. Due to system constrains, only the reverse cumulative percentage values were reported, to depict the Reverse Cumulative Distribution Plots.
The analysis was performed on the FAS-2: long term immunogenicity analysis which included all eligible participants from the V49_23 study enrolled in this extension study and provided immunogenicity data for the specific analysis at the specific timepoints.

End point type	Secondary

End point timeframe:

At Year 3, Year 4, Year 5, Year 6, Year 7, Year 8, Year 9 and Year 10 after primary series of vaccine

End point values	Conv-R/JE Group	Acc-R/JE Group	Conv-R Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	119	146	
Units: Cumulative percentage of participants				
Year 3	100	100	100	
Year 4	83	84	83	
Year 5	67	70	69	
Year 6	54	57	56	
Year 7	43	45	44	
Year 8	32	33	32	
Year 9	21	22	21	
Year 10	10	11	10	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All Cause Mortality: from Year 3 (3 years after primary series of vaccination) until completion of safety follow-up at Year 10 (10 years after primary series of vaccination); SAEs: from booster vaccination (6 to 9 months after Year 3) until Year 10

Adverse event reporting additional description:

SAEs were collected only from participants who received booster dose. Five deaths were recorded during this extension study but only one of them was reported as SAE as this was the only one that occurred in a participant who received a booster dose. Solicited and non-serious unsolicited AEs were not collected in this study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Conv-R/JE Group

Reporting group description:

Participants who completed the Rabies PrEP regimen on days 1, 8 and 29, and Japanese Encephalitis (JE) primary series regimen on days 1 and 29 in the parent study (V49_23) and, if Rabies Virus Neutralizing Antibody (RNVA) concentrations were less than (<)0.5 IU/mL, they received at least one booster dose of purified chick embryo cell culture (PCEC) rabies vaccine in this extension study.

Reporting group title	Conv-R Group

Reporting group description:

Participants who completed the Rabies PrEP regimen on days 1, 8 and 29 in the parent study (V49_23) and, if RVNA concentrations were <0.5 IU/mL, they received at least one booster dose of the PCEC rabies vaccine in this extension study.

Reporting group title	Acc-R/JE Group

Reporting group description:

Participants who completed the Rabies PrEP regimen on days 1, 4 and 8 and JE primary series regimen on days 1 and 8 in the parent study (V49_23) and, if RVNA concentrations were <0.5 IU/mL, they received at least one booster dose of the PCEC rabies vaccine in this extension study.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Solicited and non-serious unsolicited AEs were not collected in this study as the objective was to evaluate long term immunogenicity in participants who received a primary series of accelerated or conventional rabies PrEP regimens in the parent study.

Serious adverse events	Conv-R/JE Group	Conv-R Group	Acc-R/JE Group
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 44 (4.55%)	3 / 53 (5.66%)	0 / 47 (0.00%)
number of deaths (all causes)	2	1	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leiomyoma			
subjects affected / exposed	0 / 44 (0.00%)	1 / 53 (1.89%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 53 (0.00%)	0 / 47 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 44 (0.00%)	1 / 53 (1.89%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 44 (2.27%)	0 / 53 (0.00%)	0 / 47 (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
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 44 (0.00%)	1 / 53 (1.89%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Conv-R/JE Group	Conv-R Group	Acc-R/JE Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 44 (0.00%)	0 / 53 (0.00%)	0 / 47 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported