Protocol Amendment 2

Study ID: 205214

Official Title of Study: 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

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CLINICAL STUDY PROTOCOL V49_23E1 Amendment 2

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

Phase 3 PCEC Rabies Vaccine Long-term Immunogenicity and Boostability

PRO-01 TEMP 06 / Atlas No. 293620
Version No. 3 / Version Date: November 10, 2014

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Protocol Amendment 2 Rationale

Amendment number: Amendment 2

Rationale/background for changes:

- Clarification of the timeframe between each yearly Scheduled Visit: Visit 1 date has to be used as reference for calculating next visit date (e.g. Visit 1: 31 JAN 15, then Visit 2: 31 JAN 16 ± 28 days, Visit 3: 31 JAN 17 ± 28 days) *(Table 2a)*.

- Clarification of the time window between the Scheduled Clinic Visit and the Ad hoc Visit: the previous wording was not clear enough, team agreed to precise that booster administration at the Ad hoc Visit should happen between 6 to 9 months after the Scheduled Clinic Visit (*Table 2b*).

- Clarification that physical exams have to be done by practitioners in accordance with their institutional policy (*Table 2a and 2b, Section 5.1.2 Screening)*. It has been specified that collection of vital signs must be done during all Ad hoc Visits prior booster administration. During the other visits (Scheduled and Additional), they could be measured at the discretion of the investigator (*Section 5.1.2 Screening*).

- Clarification on the number of additional booster doses a subject may receive: if, after a first booster dose, the adequate RVNA level is not reached at two consecutive determinations, a subject may receive an additional booster. If he/she is still a non-responder, the investigator should manage at its discretion. (*Synopsis*; *Section 3.1 Overview of Study Design; Section 5.2 Ad hoc Clinic Visits; Section 6.3 Vaccine Preparation and Administration*).

- Clarification on premature withdrawal from the study: there was no mention on the procedure to follow in case a subject misses the Ad hoc Visit and the possible booster dose. This has been added to the relevant section, specifying that in this case the subject could come to the next following Scheduled Visit and having a blood draw according to protocol. In case RVNA concentrations <0.5 IU/mL, a booster may be given. (*Section 3.8 Premature Withdrawal from Study*).

- Clarification on Exclusion Criteria: prior to Scheduled Visit criteria have been added, as they were not previously detailed (only criteria prior to study entry and booster vaccination were stated).

Some clarification to the criteria to be checked prior the Ad hoc Visit has been added: if a subject received corticosteroids, antineoplastic and immunomodulating agents or radiotherapy within 90 days prior the Ad hoc Visit (and not prior to informed consent as previously stated) or receipt or planning to receive them during the participation to the study, they have to be withdrawn. Subjects should be excluded if they received any non-study rabies vaccine (*Section 4.2 Exclusion Criteria)*.

- Clarification on assignment of the Subject ID: this is a unique ID number and is the same as the one attributed during the parental study V49_23 (*Section 5.1.2 Screening*). It has been specified that since current year, 2019, a centralized Randomization System on internet (SBIR) has been implemented for treatment allocation. The study staff need to access the system and to enter the subject identification number for obtaining a treatment number for each subject (footnote e in *Table 2b; Section 5.1.4 Randomization; Section 6.3 Vaccine Preparation and Administration*).

- Update the name of the document used for identification of the health care practitioners to Study Staff Delegation of Responsibilities (SS DoR) (*Section 5.1.2 Screening*).

- Global rewording of *Section 7 Assessment* for simplification and clarification of the text.

- To clarify that ONLY SAEs (and the associated concomitant medications) experienced by subjects who received the rabies booster and those collected during Physical examinations must be reported period (Tables *2a* and *2b; Section 3.4.1 Data Collected from Subjects; Section 7.1.4 Serious Adverse Events*).
  Clarification of period of collection: for those subjects, SAEs and the associated concomitant medications will be collected starting from the time of booster administration until the completion of safety follow-up period (Study design and Safety Endpoint in *Synopsis*; footnote b in *Table 2a*; *Section 3.1 Overview of Study Design*; *Section 7 Assessment*; *Section 7.1.4 Serious Adverse Events*; *Section 8.1.1.1 Primary Safety Endpoints; Section 5.3.1 Follow-up Clinic Visit*). Safety follow-up period is defined as the day of the next Scheduled Clinic Visit after booster vaccination or the date of Early Termination Visit, whichever is earlier.

- To clarify the procedures for reporting AEs:
  - SAEs (and any medication or other therapeutic measures used to treat the AE) will be recorded in the eCRF as well as in the VSAE form.
  - Any AEs (e.g. after blood draw) will be recorded ONLY in the source documents (*Section 3.4.2 Tools Used for Data Collection; Section 7.1.5 Methods for Recording Adverse Events and Serious Adverse Events).*

- Rewording of the paragraph related to the recording of pre-existing event or condition that results in hospitalization for clarification purpose *(Section 7.1.5 Methods for Recording Adverse Events and Serious Adverse Events).*

- Clarification for post-study events collection: all SAEs that occur outside the protocol-specified safety follow-up period and that the investigator considers to be caused by the study vaccine must be reported to GSK or its designee (*Section 7.1.5.1 Post-Study Events).*

- Specification on vaccine preparation and administration: vaccine has to be administered intramuscularly in the deltoid area of the non-dominant arm. Alternatively, it can be administered in the deltoid area of the dominant arm if subjects experience local AEs on primary vaccination site (*Section 6.3 Vaccine Preparation and Administration*).

- Clarification on vaccine tracking at the conclusion of the study: all unused supply vaccine and supplementary labels are destroyed either locally (upon approval from Sponsor) or returned to the Sponsor or depot, as applicable (*Section 3.8 Premature Withdrawal from Study - Administrative reason; Section 6.6 Vaccine Supply, Labeling, Storage and Tracking*). Authorization for use (AFU) wording has been removed throughout the protocol as it is no longer used (*Section 6.6 Vaccine Supply, Labeling, Storage and Tracking*).

- To clarify the reporting of pregnancies:
  - Any pregnancy outcome meeting the definition of a SAE reported in <u>subjects who received booster administration</u> needs to be reported within 24 hours of the site becoming aware of the event to GSK or delegate using the VSAE Report Form and be recorded in the CRF(s). The Pregnancy Form must also be updated for further internal processing.
  - Any pregnancy outcome meeting the definition of SAEs reported in subjects <u>who have NOT received booster administration</u> need to be reported within 24 hours of the site becoming aware of the event to GSK or delegate using the VSAE

Report Form, although such SAEs will not be a part of the Clinical database and do not need to be recorded in the CRF(s). The Pregnancy Form must also be updated for further internal processing. (*Section 7.1.6 Pregnancies).*

- To correct some typographical errors.
- To update the *List of Abbreviations* and acronyms throughout the text.

PROTOCOL SYNOPSIS V49_23E1, VERSION 2.0 (Amended 25 February 2019)

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
GlaxoSmithKline Biologicals S.A.	V49_23E1	Rabies, whole virus vaccine (inactivated)

Title of Study:

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

Study Period: Approximately seven years for each individual subject.	**Clinical Phase:** 3

Background and Rationale: Rabies is an acute encephalitis due to a lyssavirus infection which is nearly always fatal (World Health Organization [WHO] 2013). Rabies is entirely preventable with the implementation of i) pre-exposure prophylaxis vaccination, for anyone who is at continual, frequent or increased risk for exposure to the rabies virus, or ii) prompt and accurate post exposure prophylaxis after suspected or proven exposure to rabies virus.

Among WHO pre-qualified rabies vaccines, Rabipur® is a highly purified, potent and efficacious chick-embryo cell vaccine indicated for active immunization against rabies in individuals of all ages. This includes pre-exposure prophylaxis, in both primary series and booster dose, and post exposure prophylaxis.

Persistence of adequate antibody concentrations for up to two years after immunization with Rabipur® was found in a limited number of GSK pre-exposure prophylaxis (PrEP) studies. According to WHO, reinforcing doses are generally required every 2-5 years and there is no evidence on the best timing for booster administration after 5 years. For this reason, the onset, extent and duration of (sero)protection and the requirement for and timing of booster vaccination following a primary series according to an accelerated or a conventional PrEP regimen deserves further investigation.

The aim of this study is to evaluate the long-term (up to approx.10 years) persistence and to assess the boostability of immune responses in subjects who received a primary series of accelerated or conventional rabies PrEP IM regimen in V49_23 study.

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals S.A.	V49_23E1	Rabies, whole virus vaccine (inactivated)

Study Objectives:

Primary Objectives:

Immunogenicity Objectives:

1. 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 subjects who received a primary series of accelerated or conventional rabies PrEP intramuscular (IM) regimen in the parent study V49_23.
2. To evaluate the antibody responses to a booster dose of Purified Chick Embryo Cell-Culture (PCEC) rabies vaccine administered to subjects with Rabies Virus Neutralizing Antibody (RVNA) concentrations <0.5 IU/mL following a primary series of accelerated or conventional rabies PrEP IM regimen in the parent study V49_23.

Safety Objective:

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.

Secondary Objective:

Immunogenicity Objective:

To evaluate the long-term (up to approx.10 years) immunogenicity in subjects who received a primary series of accelerated or conventional rabies PrEP intramuscular (IM) regimen in the parent study V49_23.

Study Design: This is a phase 3, open-label, multicenter, extension of V49_23 study in healthy adults. In the parent study (V49_23) subjects from ≥18 years to ≤65 years of age were randomized to one of four vaccination groups, three of which for rabies pre-exposure prophylaxis according to conventional (1.0 mL dose of PCEC rabies vaccine administered IM on each of days 1, 8 and 29) regimen, alone or in combination with Japanese Encephalitis (JE) vaccination according to the study group (see Table 1 below) or to a new, one-week, accelerated (1.0 mL dose of PCEC rabies vaccine administered IM on each of days 1, 4 and 8) regimen in combination with JE vaccination.

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
GlaxoSmithKline Biologicals S.A.	V49_23E1	Rabies, whole virus vaccine (inactivated)

Table 1 Vaccine Groups in Studies V49_23 and V49_23E1

V49_23 study		**V49_23E1 study**	
Study Vaccine Group	**Regimen of Primary Vaccine Administration** **N of subjects who received full PrEP and completed the study**	**Study Vaccine Group** **Maximum N of subjects who will be invited for enrollment** (at the start of the extension study)	**Regimen of Booster Vaccination**
Conventional Rabies with concomitant JE vaccination (Conv-R/JE)	**Rabies PrEP** Days 1, 8 and 29 **JE primary series** Days 1 and 29 N=158 subjects	Conv-R/JE N= up to 158 subjects	A single PCEC rabies booster dose (1.0 mL) IM for subjects with RVNA concentrations <0.5IU/mL
Accelerated Rabies with concomitant JE vaccination (Acc-R/JE)	**Rabies PrEP** Days 1, 4 and 8 **JE primary series** Days 1 and 8 N=209 subjects	Acc-R/JE N= up to 209 subjects	A single PCEC rabies booster dose (1.0 mL) IM for subjects with RVNA concentrations <0.5IU/mL
Conventional Rabies vaccination alone (Conv-R)	**Rabies PrEP** Days 1, 8 and 29 N=211 subjects	Conv-R N= up to 211 subjects	A single PCEC rabies booster dose (1.0 mL) IM for subjects with RVNA concentrations <0.5IU/mL
Conventional JE vaccination alone (Conv-JE)	**JE primary series** Days 1 and 29 N=52 subjects	NA	NA

Note: To preserve blinding in the parent study, placebo was administered at specified time points; refer to the V49_23 Protocol for details.

There will be minimum 8 Scheduled Clinic Visits for each eligible enrolled subject over 7 years.

Subjects who were randomized into one of the 3 rabies vaccination groups of the parent study V49_23, who received the full PrEP rabies regimen and completed V49_23 study following study protocol will be invited to take part to this study.

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals S.A.	V49_23E1	Rabies, whole virus vaccine (inactivated)

Subjects who were randomized to the JE conventional group in the parent study V49_23 will not be invited to take part to this extension study.

Subjects will receive their booster doses based on their individual antibody concentrations measured over time (booster will be administered only to those subjects with RVNA concentrations <0.5 IU/mL), medical history and physical examination, to ensure that they are in good health according to the investigator's opinion and meet all inclusion criteria and none of the exclusion criteria.

Blood samples (approximately 7 mL of blood at each Scheduled Clinic Visit) will be drawn in all subjects on extension study Day 1 (i.e. approximately three years [Year 3] after completion of rabies primary series in the parent study V49_23) and then at subsequent year intervals from extension study Day 1 (Year 3) onwards (Year 4, 5, 6, 7, 8, 9 and 10 after primary series in the parent study V49_23), to investigate the kinetics of RVNA concentrations.

Subjects with RVNA concentrations <0.5 IU/mL at Visit 1 of this extension study or at the following Year 4 to Year 9 annual Scheduled Clinic Visits will receive a booster immunization (a single dose of 1.0 mL to be administered intramuscularly preferably in the deltoid region of the non-dominant arm) with GSK PCEC rabies vaccine during the next Ad hoc Clinic Visit.

Subjects receiving a booster vaccination will be observed at the site for at least 30 minutes after immunization for any immediate reactions.

To investigate the prompt boostability of immune responses, additional blood samples will be drawn during Additional Clinic Visit which is approximately 7 days after the Ad hoc Clinic Visits.

During Scheduled Clinic Visit and Additional Clinic Visit, subjects will be observed for at least 15 minutes after the blood draw for any adverse event.

For subjects receiving PCEC rabies booster vaccination, Serious Adverse Events (SAEs) and the associated concomitant medications will be collected starting from the time of booster administration until ***completion of safety follow-up period (the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier)***.

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
GlaxoSmithKline Biologicals S.A.	V49_23E1	Rabies, whole virus vaccine (inactivated)

Number of Subjects planned: Up to 578 subjects, who successfully completed rabies PrEP regimens in V49_23 study and did not have protocol deviations which can impact the immunogenicity response (e.g., wrong vaccination), will be invited to participate to this extension study.

Study Population and Subject Characteristics:

Inclusion criteria: Subjects who sign***ed*** the informed consent prior to the study entry, who received the full primary vaccination series according to either the conventional rabies plus JE (Conv-R/JE), or the accelerated rabies plus JE (Acc-R/JE), or the conventional rabies (Conv-R) PrEP regimens in V49_23 study and who completed the parent study.

Exclusion criteria: Subjects with documented medical history of exposure to rabies or rabies post exposure prophylaxis after completion of the parent study (V49_23) and before V49_23E1 study start will be excluded.

Subjects who completed the parent study V49_23 but who received a wrong vaccine and/or did not receive the full 3doses of rabies vaccine following the conventional or accelerated vaccination regimen during V49_23.

The list of inclusion and exclusion criteria is included in protocol section 4.0, Selection of Study Population.

Study Procedures: Every year of the study for each subject there might be up to three different clinic visits in chronological sequence:

- Scheduled Clinic Visits, for all subjects enrolled;
- Ad hoc Clinic Visits, only for subjects with RVNA concentrations <0.5 IU/mL, (during these visits a booster dose of rabies vaccine will be administered);
- Additional Clinic Visits, only for subjects who received a booster vaccination during Ad hoc Clinic Visits.

Scheduled Clinic Visit: For all enrolled subjects there will be overall 8 blood draws (of approximately 7 mL each) scheduled during the course of the extension study; each of these blood draws will be taken at each Scheduled Clinic Visit, from extension study Day 1 (Year 3 after completion of PrEP in the parent study V49_23) and then yearly

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through Year 10.

Ad hoc Clinic Visits: Only subjects with RVNA concentrations <0.5 IU/mL at the first visit of this extension study (Day 1, Year 3) or at the following yearly Scheduled Clinic Visits (from Year 4 to Year 9) will receive a booster vaccination (a single dose of 1.0 mL to be administered intramuscularly preferably in the deltoid region of the non-dominant arm) with GSK PCEC rabies vaccine. The booster dose will be given in an "Ad hoc Clinic Visit***"*** which is planned to occur as soon as the results of the antibody assay will be available and within approximately 6 ***to 9*** months from the blood draw taken during a previous "Scheduled Clinic Visit". Prior to receipt of booster vaccination, subjects must be evaluated to confirm that they are eligible for vaccination.

Subjects who will receive a booster vaccination will be observed at the site for at least 30 minutes after vaccination for any immediate reactions and will continue yearly procedures up to Year 10.

For subjects receiving PCEC rabies booster vaccination, SAEs and the associated concomitant medications will be collected starting from the booster administration and until the day of next Scheduled Clinic Visit.

Additional Clinic Visit: To investigate the prompt boostability of the immune response, additional blood samples will be drawn approximately 7 days after the Ad hoc Clinic Visits, only for subjects who will receive booster dose of PCEC rabies vaccine.

If, after having received a booster dose, the subject does not reach the adequate antibody concentration (i.e., RVNA ≥0.5 IU/mL) at two consecutive determinations, neither at 7 days after the booster dose (i.e. Additional Clinic Visit) nor at the next yearly evaluation (i.e., Scheduled Clinic Visit), an additional booster dose may be administered at the following Ad hoc Clinic Visit. ***If the subject is still non-responder, subsequent management should be at the discretion of the investigator.***

Should a subject have RVNA concentrations below 0.5 IU/mL at blood draw performed at the final Scheduled Clinic Visit (Year 10), the ***investigator will invite the*** subject to receive a booster dose of the rabies vaccine outside the study following standard clinical practice and there will be no further analyses performed on this additional vaccination.

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals S.A.	V49_23E1	Rabies, whole virus vaccine (inactivated)

Study Vaccine: Rabipur®, purified chick-embryo cell derived (PCEC) rabies vaccine, GSK Vaccines GmbH (formerly Novartis Vaccines and Diagnostics GmbH), Marburg, Germany. After reconstitution, a booster dose consists of 1.0 mL of PCEC rabies vaccine, containing rabies virus [inactivated strain Flury Low Egg Passage (LEP)®] with a potency ≥2.5 IU/mL, and is to be administered via intramuscular (IM) injection.

Primary Endpoints:

Immunogenicity Endpoints:

The primary immunogenicity endpoints will be based on the RVNA concentrations at Year 3, 4, 5, 6, 7, 8, 9 and 10 following a primary series of accelerated or conventional rabies PrEP IM regimen during the parent study V49_23, as measured by rapid fluorescent focus inhibition test (RFFIT). RFFIT assays will be performed at a delegate, qualified laboratory, as specified by GSK.

Measures of immunogenicity will be summarized by the vaccination regimen received in the parent study V49_23, as follows:

- Time to first RVNA concentrations <0.5 IU/mL.
- Geometric Mean Concentrations (GMCs) and Geometric Mean Ratios (GMRs) for subjects receiving the booster dose, as measured by antibody concentration at 7 days after the booster dose vs. antibody concentration before the booster dose.
- Percentages of subjects with RVNA concentrations ≥0.5 IU/mL, as measured by RFFIT assay at 7 days after the booster dose and at subsequent Scheduled Clinic Visits.

Safety Endpoint:

For subjects receiving PCEC rabies booster vaccination, Serious Adverse Events (SAEs) and the associated concomitant medications will be collected starting from the time of booster administration until ***completion of safety follow-up period (the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier)***.

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
GlaxoSmithKline Biologicals S.A.	V49_23E1	Rabies, whole virus vaccine (inactivated)

Number and percentages of SAEs will be summarized only for subjects receiving a booster dose by the vaccination regimen received in the parent study V49_23 and overall.

Secondary Endpoints:

Immunogenicity Endpoints:

- Geometric Mean Antibody Concentrations (GMCs) at Year 3, 4, 5, 6, 7, 8, 9 and 10;
- Reverse Cumulative Distribution Plots (RCDPs) at Year 3, 4, 5, 6, 7, 8, 9 and 10;
- Percentages of subjects with RVNA concentrations ≥ 0.5 IU/mL, as measured by RFFIT assay at Year 3, 4, 5, 6, 7, 8, 9 and 10.

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Statistical Analyses:

Time to first RVNA concentrations <0.5 IU/mL

Kaplan-Meier estimate of the survival function, along with 95% CIs, will be computed and displayed per each vaccination regimen. The Cox regression model will be used to compare the 3 vaccine regimens every year.

Geometric Mean Concentration (GMC) and Geometric Mean Ratio (GMR)

RVNA GMCs will be based on the logarithmically transformed (base10) values.

GMCs, with the associated 95% confidence intervals will be computed for each vaccine group (assigned from parent study) at Year 3, 4, 5, 6, 7, 8, 9 and 10 by taking the exponential of the corresponding log-transformed (least squares) means and 95% confidence intervals, from an ANOVA model with fixed factors for group and center. Group differences along with 95% CIs will also be computed. Subjects will be included in this analysis until they receive the booster dose and they will be excluded thereafter.

For subjects receiving a booster dose, analysis of boostability will be conducted 7 days (and also approximately 6 ***to 9*** months) after administration of the booster dose by providing GMRs and associated 95% CIs, considering the antibody value at the booster visit as baseline (denominator) and the antibody concentration at 7 days (and also approximately ***between*** 6 ***to 9*** months) after booster as the numerator.

Reverse Cumulative Distribution Plots at Year 3, 4, 5, 6, 7, 8, 9 and 10;

Reverse cumulative distribution plots will be provided at Year 3, 4, 5, 6, 7, 8, 9 and 10 by vaccination regimen group.

Percentages of subjects with RVNA concentrations ≥0.5 IU/mL

As a form of supplementary information, also percentage of subjects with RVNA concentrations ≥0.5 IU/mL, as measured by RFFIT assay at Year 3, 4, 5, 6, 7, 8, 9 and 10 will be presented in a tabular fashion.

Interim Analyses:
In order to understand complete evolution of the antibody decay over time and the effect

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of the booster dose, every year, an immunogenicity and safety analysis will be carried out and the results will be stored in the internal clinical data repository.

Two Clinical Study Reports (CSR) are planned:

- One interim CSR will be released after all subjects will complete Scheduled Clinic Visit 4 (i.e. Year 6). This CSR will include both immunogenicity and safety analyses halfway through study. The interim CSR might be submitted to the Health Authority in case results support indication for the booster dose at a given time after the primary regimen.

- The final CSR will be released at the completion of the study and will include all study data from Visit 1 (Year 3) to Visit 8 (Year 10).

Further details regarding the interim analyses are contained in section 8.6, Interim Analyses.

Data Monitoring Committee: No Data Monitoring Committee will be convened for this study.

Table 2 Time and Events Tables

Table 2a Scheduled Clinic Visits: For All Subjects (Amended 25 February 2019)

Visit Type		**Scheduled Clinic Visit**							**Final Scheduled Clinic Visit**
Study Period		**Day 1 Year 3**	**Year 4**	**Year 5**	**Year 6**	**Year 7**	**Year 8**	**Year 9**	**Year 10**
Visit Window (Days)*		**n/a**	**-28 to +28**	**-28 to +28**	**-28 to +28**	**-28 to +28**	**-28 to +28**	**-28 to +28**	**-28 to +28**
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Event	**References**								
Screening and Safety									
Informed Consent [a]	Section 5.1.1	X							
Medical History	Section 5.1.2	X	X	X	X	X	X	X	X
Physical Exam[d]	Section 5.1.2	X	X	X	X	X	X	X	X
Exclusion/Inclusion Criteria	Section 4.0	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	Sections 5.1.2 and 6.5	X							
Assess SAEs and Relevant ***Concomitant*** Medications [b]	Sections 7.1.4, 5.1.2 and 6.5		X	X	X	X	X	X	X
Observe for at Least 15 Minutes Post Blood Draw and Assess AEs (if any)	Section 7.1.3	X	X	X	X	X	X	X	X
Immunogenicity									
Serology Blood Draw	Section 3.5	X	X	X	X	X	X	X	X
Study Completion Procedures									
Study Termination [c]	Section 5.5								X

[a] Confirm consent form signed prior to any procedures.

[b] SAEs and the associated concomitant medications will be collected ONLY from those subjects who will receive booster vaccine during ***the*** Ad hoc Clinic Visit, ***starting from the time of booster administration until completion of safety follow-up period (the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier).***

[c] Subjects who terminate the study early are recommended to complete certain study-related procedures. See section 5.5 for further details.

[d] ***Physical exams have to be done by practitioners in accordance with their institutional policy. Should the physical assessment reveal any abnormal values or events, which fall under definition of SAE, these must be documented in the CRF Adverse Events Form and reported to sponsor.***

****Visit 1 date to be used as reference for calculating next visit date (e.g. V1: 31 JAN 15, V2: 31 JAN 16 ± 28 days, V3: 31 JAN 17 ± 28 days).***

Table 2b Ad hoc and Additional Clinic Visit (Amended 25 February 2019)

Visit Type		Clinic Visit													
		Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]
Study Period		Year 3, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 1	Year 3, 7 days after Ad hoc Clinic Visit 1.1	Year 4, between 6 ***to 9*** months after Scheduled Clinic Visit 2	Year 4, 7 days after Ad hoc Clinic Visit 2.1	Year 5, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 3	Year 5, 7 days after Ad hoc Clinic Visit 3.1	Year 6, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 4	Year 6, 7 days after Ad hoc Clinic Visit 4.1	Year 7, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 5	Year 7, 7 days after Ad hoc Clinic Visit 5.1	Year 8, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 6	Year 8, 7 days after Ad hoc Clinic Visit 6.1	Year 9, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 7	Year 9, 7 days after Ad hoc Clinic Visit 7.1
Visit Window (Days)		**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**
Visit Number		**1.1**	**1.2**	**2.1**	**2.2**	**3.1**	**3.2**	**4.1**	**4.2**	**5.1**	**5.2**	**6.1**	**6.2**	**7.1**	**7.2**
Study Event	**References**														
Medical History[c]	Section 5.1.2	X		X		X		X		X		X		X	
Physical Exam[c]	Sections 5.1.2 and 5.2	X		X		X		X		X		X		X	
Pregnancy Test[c, d]	Sections 3.5 and 5.1.2	X		X		X		X		X		X		X	
Verification of Relevant Exclusion/Inclusion Criteria[c]	Section 4.0	X		X		X		X		X		X		X	
Vaccination[e]	Section 5.2	X		X		X		X		X		X		X	

Visit Type		Clinic Visit													
		Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]
Study Period		Year 3, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 1	Year 3, 7 days after Ad hoc Clinic Visit 1.1	Year 4, between 6 ***to 9*** months after Scheduled Clinic Visit 2	Year 4, 7 days after Ad hoc Clinic Visit 2.1	Year 5, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 3	Year 5, 7 days after Ad hoc Clinic Visit 3.1	Year 6, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 4	Year 6, 7 days after Ad hoc Clinic Visit 4.1	Year 7, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 5	Year 7, 7 days after Ad hoc Clinic Visit 5.1	Year 8, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 6	Year 8, 7 days after Ad hoc Clinic Visit 6.1	Year 9, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 7	Year 9, 7 days after Ad hoc Clinic Visit 7.1
Visit Window (Days)		**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**
Visit Number		**1.1**	**1.2**	**2.1**	**2.2**	**3.1**	**3.2**	**4.1**	**4.2**	**5.1**	**5.2**	**6.1**	**6.2**	**7.1**	**7.2**
Study Event	**References**														
30 Minutes Post Booster Injection Assessment	Section 5.2.1	X		X		X		X		X		X		X	
Assess SAEs and Relevant ***Concomitant*** Medications[f]	Sections 7.1.4, 5.1.2 and 6.5	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity															
Serology Blood Draw	Section 3.5		X		X		X		X		X		X		X
Observe for at Least15 Minutes Post Blood Draw and Assess AEs (if any)	Section 7.1.3		X		X		X		X		X		X		X

Visit Type		Clinic Visit													
		Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]
Study Period		Year 3, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 1	Year 3, 7 days after Ad hoc Clinic Visit 1.1	Year 4, between 6 ***to 9*** months after Scheduled Clinic Visit 2	Year 4, 7 days after Ad hoc Clinic Visit 2.1	Year 5, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 3	Year 5, 7 days after Ad hoc Clinic Visit 3.1	Year 6, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 4	Year 6, 7 days after Ad hoc Clinic Visit 4.1	Year 7, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 5	Year 7, 7 days after Ad hoc Clinic Visit 5.1	Year 8, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 6	Year 8, 7 days after Ad hoc Clinic Visit 6.1	Year 9, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 7	Year 9, 7 days after Ad hoc Clinic Visit 7.1
Visit Window (Days)		**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**
Visit Number		**1.1**	**1.2**	**2.1**	**2.2**	**3.1**	**3.2**	**4.1**	**4.2**	**5.1**	**5.2**	**6.1**	**6.2**	**7.1**	**7.2**
Study Event	**References**														

[a] Ad hoc Clinic Visit (which is planned to occur as soon as the results of the antibody assay will be available and within approximately 6 ***to 9*** months from the blood draw taken during a previous "Scheduled Clinic Visit") is only applicable for those subjects with RVNA concentrations <0.5 IU/mL during this extension study. See sections 3.1 and 3.9 for further details.

[b] Additional Clinic Visit (within approximately 7 days from Ad hoc Clinic Visit) only applicable for subjects who will receive a booster dose of PCEC rabies vaccine during Ad hoc Clinic Visit.

[c] Procedure to be performed prior to vaccination. ***Physical exams have to be done by practitioners in accordance with their institutional policy. Should the physical assessment reveal any abnormal values or events, which fall under definition of SAE, these must be documented in the CRF Adverse Events Form and reported to sponsor.***

[d] Only for female subject of childbearing potential who are eligible to receive the booster dose.

[e] ***GSK Biologicals' Randomization System on Internet (SBIR) will be used for Treatment allocation.***

[f] SAEs and the associated concomitant medications will be collected starting from the booster administration until the ***completion of safety follow-up period (the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier)***.

LIST OF ABBREVIATIONS (Amended 25 February 2019)

AE	Adverse ***E***vent
CBER	Center for Biologics Evaluation and Research
CCEEVs	Cell Culture or Embryonated Egg-Based rabies Vaccines
CI	Confidence Interval
CRO	Contract Research Organization
CSR	Clinical Study Report
eCRF	***electronic*** Case Report Form
EC	Ethic Committee
EDC	Electronic Data Capture
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practices
GMC	Geometric Mean Concentration
GMR	Geometric Mean Ratio
HR	***Hazard Ratios***
ICF	Informed Consent Form
ICH	International Conference ***for*** Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification (Subject ID)
IM	Intramuscular
IRB	Institutional Review Board

IU	International Unit
KM	***Kaplan-Meier***
MedDRA	Medical Dictionary for Regulatory Activities
mg	***Milligram***
mL	Milliliter
PCEC	Purified Chick-Embryo Cell Culture
PEP	Post Exposure Prophylaxis
PrEP	Pre-Exposure Prophylaxis
RCDP	Reverse Cumulative Distribution Plots
RFFIT	Rapid Fluorescent Focus Inhibition Test
RVNA	Rabies Virus Neutralizing Antibodies
SAE	Serious Adverse Event
SBIR	***Source DataBase for Internet Randomization***
SmPC	***Summary of Product Characteristics***
WHO	World Health Organization

1.0 BACKGROUND AND RATIONALE

1.1 Background (Amended 25 February 2019)

Rabies is a disease caused by the rabies virus (family Rhabdoviridae, genus *Lyssavirus*), which is shed in the saliva of infected and symptomatic animals. The transfer via a bite from an infected animal is the most efficient route of transmission. Upon transmission and after a variable incubation period, it migrates to the central nervous system and leads to an acute, progressive encephalomyelitis that is nearly always fatal. The incubation period in humans is usually several weeks to months, but ranges from <1 week to >1 year (***World Health Organization [***WHO***]*** 2013). Without intensive care, death occurs within 2 weeks after the appearance of clinical symptoms (WHO 2013).

Rabies occurs in more than 150 countries and territories, indicating its worldwide presence. More than 60,000 people die of rabies every year and 95% of these deaths occur in Asia and Africa (WHO 2013). Rabies has in fact the highest case fatality ratio of any currently recognized infectious disease, being almost always fatal (WHO 2013).

Pre-exposure (PrEP) or post exposure prophylaxis (PEP) as per the recommend regimens are the only means of protection against rabies virus infection.

Pre-exposure prophylaxis is recommended for anyone who is at continual, frequent or increased risk for exposure to the rabies virus, as a result of ***her/his*** residence or occupation, including travelers in high-risk areas (WHO 2013).

Post-exposure prophylaxis: after suspected or proven exposure to rabies virus, prompt use of modern cell culture or embryonated egg-based rabies vaccines (CCEEVs) with proper wound management and simultaneous administration of rabies immunoglobulin (depending on the category of exposure) is almost invariably effective in preventing rabies, even after severe exposure (WHO 2013).

Protection against rabies is dependent on the presence of ***R***abies ***V***irus ***N***eutralizing ***A***ntibodies (RVNA). WHO recommended method to measure RVNA serum concentrations is Rapid Fluorescent Focus Inhibition Test (RFFIT). A neutralizing antibody titer of ≥0.5 IU/mL is regarded by the WHO as being an 'adequate' antibody response following rabies vaccination, and is used as a threshold in clinical trials.

Rabipur® is a ***P***urified ***C***hick-***E***mbryo ***C***ell ***C***ulture (PCEC) rabies vaccine indicated for active immunization against rabies in individuals of all ages. This includes pre-exposure prophylaxis (i.e. before possible risk of exposure to rabies), in both primary series and booster dose, and post exposure prophylaxis (i.e. after suspected or proven exposure to rabies).

The target subjects for this study have already received a primary series of PrEP with Rabipur® either following a conventional (days 1, 8 and 29) regimen alone or in combination with JE vaccination or following an accelerated (days 1, 4 and 8) regimen in combination with JE vaccination in the parent study V49_23.

Although in clinical trials persistence of adequate antibody concentrations for 2 years after immunization with Rabipur® without additional booster has been observed in 100% of subjects, and experience shows that Rabipur® booster doses are generally required every 2-5 years following the conventional PrEP regimen, as recommended by WHO and following current Rabipur® ***Summary of Product Characteristics (SmPC)***, the requirement for and the timing of booster vaccination following an accelerated pre-exposure prophylaxis regimen have never been evaluated previously and will be characterized in this study.

1.2 Rationale

The purpose of this study is to evaluate the long-term (up to approx.10 years after primary series for PrEP) persistence and to assess the boostability of immune responses in subjects who participated and completed V49_23 study and received either the full primary vaccination series according to the conventional rabies plus JE (Conv-R/JE), or the accelerated rabies plus JE (Acc-R/JE), or the conventional rabies (Conv-R) PrEP alone regimens.

2.0 OBJECTIVES

2.1 Primary Objectives

Immunogenicity Objectives

3. 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 subjects who received a primary series of accelerated or conventional rabies PrEP intramuscular (IM) regimen in the parent study V49_23.
4. To evaluate the antibody responses to a booster dose of PCEC rabies vaccine administered to subjects 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.

Safety Objective

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.

2.2 Secondary Objective

Immunogenicity Objective:

To evaluate the long-term (up to approx.10 years) immunogenicity in subjects who received a primary series of accelerated or conventional rabies PrEP IM regimen in the parent study V49_23.

3.0 STUDY DESIGN

3.1 Overview of Study Design (Amended 25 February 2019)

Introduction of study design:

This is a phase 3, open-label, multicenter, extension of V49_23 study in adult subjects.

In the parent study (V49_23) subjects from ≥18 years to ≤65 years of age were randomized to one of four vaccination groups, three of which for rabies pre-exposure prophylaxis according to conventional (1.0 mL dose of PCEC rabies vaccine administered IM on each of days 1, 8 and 29) alone or in combination with Japanese Encephalitis (JE) vaccination or according to a new, one-week, accelerated (1.0 mL dose of PCEC rabies vaccine administered IM on each of days 1, 4 and 8) regimen in combination with JE vaccination depending on the study group (see Table 3.1-1).

Subjects who were randomized into one of the 3 rabies vaccination group regimen***s***, who received the full PrEP rabies regimen and completed V49_23 following study protocol will be invited to take part to this study.

Subjects who were randomized to the JE conventional group in V49_23 study will not be invited to take part to this extension study.

Table 3.1-1 Vaccine Groups in Studies V49_23 and V49_23E1

V49_23 study		**V49_23E1 study**	
Study Vaccine Group	**Regimen of Primary Vaccine Administration** **N of subjects who received full PrEP and completed the study**	**Study Vaccine Group** **Maximum N of subjects who will be invited for enrollment** (at the start of the extension study)	**Regimen of Booster Vaccination**
Conventional Rabies with concomitant JE vaccination (Conv-R/JE)	**Rabies PrEP** Days 1, 8 and 29 **JE primary series** Days 1 and 29 N=158 subjects	Conv-R/JE N= up to 158 subjects	A single PCEC rabies booster dose (1.0 mL) IM for subjects with RVNA concentrations <0.5IU/mL
Accelerated Rabies with concomitant JE vaccination (Acc-R/JE)	**Rabies PrEP** Days 1, 4 and 8 **JE primary series** Days 1 and 8 N=209 subjects	Acc-R/JE N= up to 209 subjects	A single PCEC rabies booster dose (1.0 mL) IM for subjects with RVNA concentrations <0.5IU/mL

V49_23 study		V49_23E1 study	
Conventional Rabies vaccination alone (Conv-R)	**Rabies PrEP** Days 1, 8 and 29 N=211 subjects	Conv-R N= up to 211 subjects	A single PCEC rabies booster dose (1.0 mL) IM for subjects with RVNA concentrations <0.5IU/mL
Conventional JE vaccination alone (Conv-JE)	**JE primary series** Days 1and 29 N=52 subjects	NA	NA

Up to 578 subjects, who completed rabies PrEP regimens in the parent study V49_23 will be invited to participate to this extension study.

All sites will be trained in a uniform fashion and th***ose*** sites will be monitored to ensure consistency in study execution across all centers.

Informed consent will be performed prior to any study-related procedures.

Subjects who sign the informed consent will be screened to assess for their eligibility of participation in the study.

All individuals who are screened for the study, as defined in this section, should be recorded on the "subject screening log" where information on the selection of potential participants in the trial should be collected. The reason why an individual was not enrolled, the enrollment date and assigned subject number and code which is carried over from the parent study, should be recorded by the investigator/study staff. It is the responsibility of the investigator/delegate to file this document among those of the Investigator Site File to be readily available for on-site monitoring and/or for inspection by the relevant authorities.

Subjects will receive their booster doses based on their own antibody concentrations (booster will be administered only to those subjects with RVNA concentrations <0.5 IU/mL), medical history and physical examination to ensure that they are in good health according to the investigator's opinion and meet all inclusion criteria and none of the exclusion criteria.

For all subjects enrolled there will be overall 8 blood draws (of approximately 7 mL each) scheduled during the course of the extension study; each of these blood draws will be taken at each Scheduled Clinic Visit, from extension study Day 1 (Year 3 after completion of PrEP in the parent study V49_23) and then yearly through Year 10. During

Scheduled Clinic Visit and Additional Clinic Visit, subjects will be observed for at least 15 minutes after the blood draw for any adverse event (AE).

A urine pregnancy test will be performed for female subject of childbearing potential who are eligible to receive the booster dose prior to vaccination.

Vaccination procedures:

Only those subjects for which the RVNA concentration determined to be <0.5 IU/mL based on the blood sample from Visit 1, 2, 3, 4, 5, 6, and 7 (i.e., on Year 3, 4, 5, 6, 7, 8, and 9) will receive the booster dose of rabies vaccine in an open label fashion, ***t***ime of each booster dose and blood draw for rabies antibody concentrations needs to be meticulously recorded.

If, after having received a booster dose, the subject does not reach the adequate antibody concentration of 0.5 IU/mL at two consecutive determinations, neither at 7 days after the booster dose (i.e. Additional Clinic Visit) nor at the next yearly evaluation (i.e. Scheduled Clinic Visit), an additional booster dose may be administered at the following Ad hoc Clinic Visit. ***If the subject is still non-responder, subsequent management should be at the discretion of the investigator.***

Should a subject have RVNA concentrations below 0.5 IU/mL at blood draw performed at the final Scheduled Clinic Visit (Year 10), the ***investigator will invite the subject*** to receive a booster dose of the rabies vaccine outside the study following standard clinical practice and there will be no further analyses performed on this additional vaccination.

Such subject will receive 1.0 mL single dose (freeze-dried powder + diluent [sterile water]) for reconstitution and injection of the rabies vaccine intramuscularly.

Post-vaccination evaluations:

The safety data will be collected only from those subjects who received booster dose of rabies vaccine during any Ad hoc Clinic Visit.

The safety data in these subjects will include;

- At least 30 minutes post-vaccination: ***t***he subject will be observed by the investigator/delegate at the clinical trial site for any immediate reaction and it will be documented in subject's source document.
- Starting from the time of booster administration until ***completion of safety follow-up period (the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier)*** SAEs and the associated

concomitant medications will be recorded by interviewing the subject during next ***C***linic ***V***isit and based on the subject's medical records.

To investigate the prompt boostability of the immune response, during Additional Clinic Visits additional blood samples will be drawn approximately 7 days after the booster dose only from those subjects who received PCEC rabies booster vaccine during previous Ad hoc Clinic Visits.

In order to understand complete evolution of the antibody decay over time and the effect of the booster dose, every year, an immunogenicity and safety analysis will be carried out and the results will be stored in the internal clinical data repository.

Two Clinical Study Reports (CSR) are planned:

- One interim CSR will be released after all subjects will complete Scheduled Clinic Visit 4 (i.e. Year 6). This CSR will include both immunogenicity and safety analyses halfway through the study. The interim CSR might be submitted to the Health Authority in case results support indication for the booster dose at a given time after the primary regimen.

- The final CSR will be released at the completion of the study and will include all study data from Visit 1 (Year 3) to Visit 8 (Year 10).

A listing with individual subject antibody titers will be generated by the sponsor to show which subjects have rabies neutralizing antibody concentrations <0.5 IU/mL and thus qualify to be vaccinated with a booster dose of rabies vaccine during the Ad hoc Clinic Visit. The decision will be based on RVNA concentration from the blood sample taken in the previous Scheduled Clinic Visits (e.g. booster administration at the Ad hoc Clinic Visit 1.1 for subjects with RVNA concentrations ***<0.5 IU/mL at the Scheduled Clinic Visit 1***).

3.2 Study Period

Each subject should expect to participate in the study for approximately 7 years, from the time of enrolment through the last study visit.

3.3 Blinding Procedures

This is an open label study. The laboratory that will perform the serology analysis will be blinded to treatment arm.

3.4 Data Collection (Amended 25 February 2019)

3.4.1 Data Collected from Subjects

The following data will be collected from each subject over the duration of their study participation:

- Demographic Information.
- Medical History.
- Concomitant Medications ***(only when associated to a SAE).***

'Booster vaccination information', 'pregnancy test results of women of childbearing potential' and SAEs will be collected from those subjects who will receive booster dose of rabies vaccine.

All data collected must only be identified using the GSK Subject ID.

3.4.2 Tools Used for Data Collection

Data will be recorded in the subject's source record and collected on eCRFs.

Any safety information either within 30 minutes of post vaccination and/or up to the day of next Scheduled Clinic Visit ***and which can be considered an AE*** must be recorded in subject's source document and it must be described as a verbally reported adverse event.

Any AE ***that occurs during the specified safety collection period*** which fulfils any of the seriousness criteria mentioned in section 7.1.4 must be reported to the sponsor ***via the Vaccines Serious Adverse Event (VSAE) Form which is part of the Investigator Site File*** and therefore entered on the Adverse Event CRF.

Any adverse event that is considered to be caused by the study vaccine and occurs outside the protocol-specified follow-up period should be reported to the sponsor (section 7.1.5.1, Post-study events).

3.5 Collection of Clinical Specimens

The following clinical specimens are required to be collected from each subject in this study:

- Blood.
- Urine (Only for female subjects of childbearing potential eligible for booster).

Processing of each blood sample should be completed by a qualified site member and in accordance with the study-specific Clinical Specimen Laboratory Manual. Immunological assays will be performed by a GSK or designated, qualified laboratory. Refer to the study-specific Clinical Specimen Laboratory Manual for additional details.

Blood Specimens

A minimum of approximately 7 mL sample of blood will be drawn from all subjects at Scheduled Clinic Visits 1, 2, 3, 4, 5, 6, 7 and 8 (i.e., Year 3, 4, 5, 6, 7, 8, 9, and 10).

In addition, minimum of approximately 7 mL sample of blood will be drawn at Additional Clinic Visits 1.2, 2.2, 3.2, 4.2, 5.2, 6.2, and 7.2 **only** from those subjects who received booster vaccine during the previous Ad hoc Clinic Visit. The blood volume will not exceed 7 mL at each time point in order to provide the necessary serum volume (approximately half of the blood draw volume) for the serology assays.

The blood will be used for immunological assays. See section 7.0, Assessments for additional details.

The total amount of blood collected over the study period per subject will be maximum up to 105 mL over 7 years.

Urine Specimens

To confirm the pregnancy status, urine will be collected for pregnancy testing in those females of child bearing potential who are eligible to receive the booster dose at Ad hoc Clinic Visits i.e. Visit 1.1, 2.1, 3.1, 4.1, 5.1, 6.1, and 7.1 before vaccination. The pregnancy test will be performed at the study site.

3.6 Stopping/Pausing Guidelines

There are no predetermined stopping rules other than circumstances for which subjects may not be eligible for additional study vaccinations as described in section 4.0, Selection of Study Population or may be withdrawn from the study according to the best interests of the subject as described in section 3.8, Premature Withdrawal from Study.

3.7 Data Monitoring Committee

Data Monitoring Committees (DMCs) will not be utilized for this study.

3.8 Premature Withdrawal from Study (Amended 25 February 2019)

Subjects may withdraw at any time, or be dropped from the study at the discretion of the investigator should any untoward effects occur and/or for safety reasons. In addition, a subject may be withdrawn by the investigator or the Sponsor if he/she violates the study plan or for administrative reasons. The investigator or study coordinator must notify the Sponsor immediately when a subject has been withdrawn due to an adverse event.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The investigator should make every attempt to evaluate the subject's safety, including resolution of ongoing AEs, at the time of premature withdrawal. When a subject withdraws, or is withdrawn, from the study, the procedures described in section 5.5.1, Early Termination Visit should be completed if possible.

The reasons for premature withdrawal from the study include: Adverse event, death, withdrawal of consent, lost to follow-up, administrative reason, and protocol deviation. These reasons are described in greater detail below. Since these subjects will be considered censored for purposes of analysis, the time of their premature withdrawal should be meticulously recorded.

Adverse Event

For any subject withdrawn from study participation prior to the planned Study Termination Visit, it is important to determine if an AE was associated with the reason for discontinuing the study. This AE must be identified on the AE CRF page by indicating "Withdrawn from study due to AE". Any ongoing AEs at the time of study withdrawal must be followed until resolution or stabilization.

Subjects who develop a serious adverse event (SAE) judged to be possibly or probably related to the study vaccine, including hypersensitivity reactions, should not receive subsequent vaccination even if subject's RVNA concentration is found to be <0.5 IU/mL based on the next yearly serology analysis.

Death

For any subject withdrawn from study participation due to death, this should be noted on the Study Termination CRF page and it should be notified to the Sponsor. For subjects who received a booster dose, which withdraw from the study due to death during the safety observation period (from the booster administration and until the day of next Scheduled Clinic Visit), the associated SAE that led to the death must be reported.

Withdrawal of consent

The subject or legal guardian can withdraw consent for participation in the study at any time without penalty or loss of benefit to which the subject is otherwise entitled. Reason for early termination should be deemed as "withdrawal of consent" if the subject withdraws from participation due to a non-medical reason (i.e., reason other than AE). If the subject requests complete withdrawal from the study, no further study interventions will be performed with the subject.

Lost to Follow-Up

For subjects who fail to show up for final ***Scheduled C***linic ***V***isit, or for three consecutive Scheduled Clinic Visits, study staff are encouraged to make at least three documented attempts to contact the subject by telephone and at least one documented written attempt to contact the subject or legal guardian to encourage the completion of study termination procedures. ***In case an Ad hoc Visit is missed, the subject could come to the next following Scheduled Visit and having a blood draw according to protocol. In case RVNA concentrations <0.5 IU/mL, a booster may be given according to protocol.*** These efforts to contact the subject should be recorded in the source document. The termination date for the subject to be captured on the Study Termination CRF page is the date of the last successful contact (clinic visit or telephone) with the subject.

Administrative Reason

Examples for subjects withdrawn from the study due to administrative reason can include: Sponsor decision to terminate the study, subject meeting a pre-specified withdrawal criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the Study Termination CRF page and any ongoing SAEs at the time of study withdrawal must be followed until resolution/stabilization.

If the clinical study is prematurely terminated by the Sponsor, the investigator is to promptly inform the study subjects and local ***IRB/EC (Institutional Review Board/ Ethic Committee)*** and should assure appropriate therapy and follow up for the subjects. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/vaccines, etc.) must be ***destroyed either locally or*** returned to the Sponsor ***or depot, as applicable.***

For subjects who are withdrawn from the study due to receipt of an excluded medication/vaccination or due to significant protocol non-compliance, this reason should be noted in the Study Termination CRF page.

Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardizes the subject's health, safety, or rights.

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact GSK or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by GSK and approved by the IRB/EC and health authorities it cannot be implemented.

Any subject who becomes pregnant during the study, despite the protocol requirement for adequate contraception, will not receive further vaccination until delivery but should be encouraged to continue participating in the study. The site must complete a Pregnancy Report CRF (initial report) as soon as possible after learning of pregnancy occurrence (see section 7.1.6, Pregnancies for further details).

If the subject withdraws from the study for any of the above categories except death, the site will obtain permission from the subject to continue to remain in contact with her until the outcome of the pregnancy is known, even if the outcome is not known until after the subject reaches the end of follow-up period.

3.9 End of Study

Most clinical trials intended to support the immunogenicity and safety of an Investigational Product proceed to full completion of planned sample size accrual.

Evaluation of the primary immunogenicity objectives requires the testing of biological samples from the study subjects, which can only be completed after all samples are collected. The last samples for the analysis of the primary objectives will be taken at Visit 8. For the purpose of this protocol, end of study is defined as the completion of the testing of such biological samples, to be achieved no later than 8 months after collection of the last biological sample at the Scheduled Clinic Visit 8 (Year 10).

Should a subject have RVNA concentrations below 0.5 IU/mL at blood draw performed at the final Scheduled Clinic Visit (Year 10), the subject will be invited to receive a booster dose of the rabies vaccine outside the study following standard clinical practice and there will be no further analyses performed on this additional vaccination.

4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

In order to participate in this study, all subjects must meet ALL of the inclusion criteria described.

1. All individuals who were randomized to Conventional Rabies and JE vaccination or to Accelerated Rabies and JE vaccination or to Conventional Rabies groups during the parent study, who received the full PrEP regimen and completed the trial following V49_23 study protocol.
2. Individuals who have voluntarily given written informed consent after the nature of the study has been explained according to local regulatory requirements, prior to study entry.
3. Individuals who can comply with study procedures[1].
4. Males
   Or
   Females of non-childbearing potential[2]
   Or
   Females of childbearing potential who are using an effective birth control method[3] which they intend to use for at least 6 months after the booster vaccination. This criterion is applicable only for those subjects who receive a booster dose.

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[1] A subject *and* legal guardian is considered to be compliant if the Investigator judges that the subject will return for all the clinical visits as scheduled in the study.

[2] A female is considered to be of non-childbearing potential prior to menarche and after natural or induced menopause. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea for which there is no other obvious pathological or physiological cause. Induced menopause is recognized to have occurred after hysterectomy, after bilateral oophorectomy, or iatrogenic ablation of ovarian function.

[3] The following birth control methods are considered effective:

- Abstinence
- Hormonal contraceptive (such as oral, injection, transdermal patch, implant) if used for at least 30 days prior to informed consent or booster vaccination
- Diaphragm with spermicide, tubal occlusion device
- Intrauterine device (IUD)
- Tubal ligation
- Male partner using condom with spermicide
- Male partner having been vasectomized at least six months prior to informed consent or booster vaccination

Prior to receipt of booster vaccination during Ad hoc Clinic Visit, subjects must be evaluated to confirm that they are eligible. If subjects do not meet any of the original inclusion criteria listed above, they should not receive booster dose of rabies vaccine.

4.2 Exclusion Criteria (Amended 25 February 2019)

Prior to extension study entry, each subject must not have:

1. Completed the parent study V49_23 without receiving the full 3 rabies vaccine doses following the assigned pre-exposure prophylaxis regimen.
2. History of exposure to suspected or confirmed rabid animal.
3. Receipt of rabies immunoglobulins, rabies post exposure prophylaxis following completion of V49_23 study.
4. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.
5. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
6. Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to informed consent or planning to receive them during the participation to the study.
7. Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent or planning to receive them during the participation to the study.
8. Received immunoglobulins or any blood products within 180 days prior to informed consent or planning to receive them during the participation to the study.
9. Study personnel as well as their immediate family or household member.
10. Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.

Prior to Scheduled Visit, each subject must not have:

1. ***History of exposure to suspected or confirmed rabid animal.***
2. ***Receipt of rabies immunoglobulins, non-study rabies vaccine following completion of V49_23 study.***
3. ***Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.***

4. ***Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.***
5. ***Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to informed consent or planning to receive them during the participation to the study.***
6. ***Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent or planning to receive them during the participation to the study.***
7. ***Received immunoglobulins or any blood products within 180 days prior to informed consent or planning to receive them during the participation to the study.***
8. ***Study personnel as well as their immediate family or household member.***
9. ***Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.***

Prior to booster vaccination, each subject eligible for booster vaccination (i.e., subjects with RVNA concentrations <0.5 IU/mL at the first visit of this extension study [Day 1, Year 3] or at the following year visits [Year 4 to Year 9]) should be in good health status and must not have none of the following:

1. Progressive, unstable or uncontrolled clinical conditions.
2. Abnormal function of the immune system resulting from:
   a. Clinical conditions.
   b. Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior ***the Ad hoc visit*** or receipt or planning to receive them during the participation to the study.
   c. Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior ***the Ad hoc visit*** or receipt or planning to receive them during the participation to the study.
3. ***Receipt of non-study rabies vaccine.***
4. Receipt of any other vaccines within 28 days prior to the booster dose or planning to receive any vaccine within 28 days from the booster dose.
5. Receipt of any investigational or non-registered medicinal product within 14 days before booster dose till next Scheduled Clinic Visit after booster dose administration.
6. Receipt of anti-malarial medications (e.g. Mefloquine) within 14 days before booster dose till next Scheduled Clinic Visit after booster dose administration.

Prior to receipt of booster study vaccination, subjects must be evaluated to confirm that they are in good health and they are eligible for subsequent vaccination. If subjects meet any of the original exclusion criteria listed above, they should not receive additional vaccinations.

4.3 Criteria for Delay of Vaccination

There may be instances when individuals meet all eligibility criteria for booster vaccination yet have a transient clinical circumstance which may warrant delay of booster vaccination: body temperature elevation [≥38.0° C (≥ 100.4° F) within 3 days prior to intended booster study vaccination], or use of antipyretics and/or analgesic medications within 24 hours prior to vaccination. Under such circumstances, a subject may be considered eligible for booster vaccination after resolution of the acute febrile illness has occurred and inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

5.0 STUDY PROCEDURES (Amended 25 February 2019)

The sections that follow provide an overview of the procedures that ***have*** to be followed in enrolling, evaluating, and following subjects who participate in this clinical study. Visits can be either Scheduled Clinic Visits or Ad hoc Clinic Visits or Additional Clinic Visits, as specified in the Table below and in the Time and Events Tables 2a and 2b.

Table 5.0-1 Study Procedures

Visit Category	Procedures
Scheduled Clinic Visits (or pre-vaccination clinic visits)	Section 5.1 describes procedures to be followed prior to study vaccination: informed consent/assent, screening, enrolment, randomization, blood draw, as applicable.
Ad hoc Clinic Visits (or vaccination clinic visits)	Section 5.2 describes procedures to be followed during each clinic visit involving booster vaccination: vaccination and post-vaccination procedures.
Additional Clinic Visits (or post-vaccination clinic visits)	Section 5.3 describes follow-up clinic visits for those subjects who received a booster vaccination.
Unscheduled Visit(s)	Section 5.4 describes possible procedures to be followed at unscheduled clinic visits.
Study Termination Visit	Section 5.5 describes procedures to be followed at the last study visit for a subject (may include early termination visit).

5.1 Scheduled Clinic Visits - Pre-vaccination Clinic Visit(s)

This section describes the procedures that must be performed for each potential subject prior to enrollment, including obtaining informed consent and screening.

5.1.1 Informed Consent

"Informed consent" is the voluntary agreement of an individual or his/her legal guardian(s) to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision.

Informed consent following local IRB/EC guidance **must** be obtained before conducting any study-specific procedure (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent.

If a subject or legal guardian is unable to read, an impartial witness should be present during the entire informed consent discussion. An impartial witness is defined as a person who is independent from study conduct, who cannot be unfairly influenced by those involved with the study, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or legal guardian and after the subject or legal guardian has verbally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by the subject or legal guardian and that informed consent was freely given by the subject or legal guardian.

5.1.2 Screening

After an individual has consented to participate in the study and informed consent is signed, that individual ***will be assigned a unique Subject ID which she/he is carrying from V49_23 study (the parent study)***. The subject's unique Screening Number will be documented in the Screening and Enrolment log. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in section 4.0, Selection of Study Population and evaluated during this screening procedure.

Prior to study enrolment, demographic data will be collected from the subject, including: gender, height and weight.

Medical history will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for study participation such as prior vaccinations against a specific disease, concomitant medications, and previous and ongoing illnesses or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem.

Review of systems is a structured interview that queries the subject or legal guardian as to any complaints the subject has experienced across each organ system. This will be performed before enrolment and used to guide physical examination.

If applicable, prior and concomitant medications or vaccinations taken prior to start of study should be collected (refer to section 6.5, Prior and Concomitant Medications and Vaccines for further details).

Collect***ion of*** vital signs (heart rate, respiratory rate, blood pressure, and temperature) ***has to be done during all Ad hoc Visits prior booster administration. At Scheduled and Additional Visits, their measurement should be at the discretion of the investigator.***

A general physical examination is to be performed by a qualified health care practitioner, ***in accordance with their institutional policy***. "Qualified health care practitioner" refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the ***Study Staff Delegation of Responsabilities (SSDoR)***.

These data will be written in the source document (see section 9.1, Source Documentation). Should the physical assessment reveal any abnormal values or events, which fall under definition of SAE, these must be documented in the CRF Adverse Events Form and reported to sponsor.

On the first Scheduled Clinic Visit, approximately 7 mL of blood will be drawn from all subjects for the serology testing (Refer to section 3.5, Collection of Clinical Specimens) and the subjects will be observed for at least 15 minutes after the blood draw for any AE. Record any such observation in the subject's source document only and not in the eCRF.

In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log. If the individual is determined to be eligible for the study, he/she will be enrolled into the study.

5.1.3 Enrolment

After signing the informed consent form, if an individual is determined to be eligible for study participation, the investigator will enroll the subject into the EDC ***(Electronic Data Capture)*** system.

5.1.4 Randomization

This is a non-randomized extension study. Enrolled subjects will be manually assigned a unique Subject ID which they are carrying from V49_23 study (the parent study). The Subject ID will be the subject's unique identification number for all CRFs and associated study documentation that will be used for duration of the study. The Screening Number ceases to be used and remains in the Screening and Enrolment Log only.

Subject numbers (ID) will be pre-loaded into a centralized Randomization System on internet (SBIR).

If for any reason, after enrolment the subject fails to undergo study procedures this is an Early Termination and the reason should be recorded in source document as specified in the Source Data Agreement. The information on these Early Termination subjects should be kept distinct in the source documentation from subjects who are screen failures, as described in section 5.1.2, Screening.

5.2 Ad Hoc Clinic Visit(s) - Vaccination Clinic Visit(s)

The first dose of booster vaccination with rabies vaccine will be performed in a clinical visit occurring as soon as the results of the antibody assay will be available and within approximately 6 ***to 9*** months from the blood draw taken during Scheduled Clinic Visit 1 (Day1); it is termed as "Ad hoc Clinic Visit" 1.1.

Only for those subjects with RVNA concentrations <0.5 IU/mL at the first visit of this extension study (Day 1, Year 3) or at the following yearly visits (Year 4 to Year 9) a booster dose of PCEC rabies vaccine will be administered during the next planned Ad ***h***oc Clinic Visit.

Should the subject be a low responder to a booster dose of the rabies vaccine provided during this extension study and not achieve adequate antibody concentrations following a booster injection neither at 7 days (following the blood drawn at the "Additional Clinic Visits" after the booster) nor at the next evaluation (following the blood drawn at the "Scheduled Clinic Visits" after the booster), a subsequent booster dose may be administered at the subsequent "Ad hoc Clinic Visit". ***If the subject is still non-responder, subsequent management should be at the discretion of the investigator.***

Should a subject have RVNA concentrations below 0.5 IU/mL at blood draw performed at the final Scheduled Clinic Visit (Year 10), the subject will be invited to receive a booster dose of the rabies vaccine outside the study following standard clinical practice and there will be no further analyses performed on this additional vaccination.

After completing the pre-vaccination procedures during Ad hoc Clinic Visit, administer the vaccine to the subject according to the procedures described in section 6.3, Vaccine Preparation and Administration.

Prior to administration of booster vaccination during Ad hoc Clinic Visit, confirm that the subject is eligible to receive booster study vaccination and does not meet any criteria for delaying of study vaccination as described in section 4.0, Selection of Study Population.

5.2.1 Post-vaccination Procedures

The following post-vaccination procedures will be performed on Ad hoc Clinic Visits.

After vaccination, the subject will be observed for at least 30 minutes for any AEs. Record all safety data collected during this time in the subject's source document. If an AE fulfils any of the seriousness criteria mentioned in section 7.1.4 it must be reported to the sponsor and therefore entered on the Adverse Event CRF.

The site should schedule with the subject or legal guardian the next subject study activity, the Additional Clinic Visit.

The subject or legal guardians should be reminded of the next planned study activity. The subject or legal guardian will be reminded to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.2.2 Post-vaccination Reminder Calls

Not applicable.

5.3 Additional Clinic Visit(s) - Post-vaccination Visit(s)

Post-vaccination visits will be performed approximately 7 days after a subject received booster dose of rabies vaccine.

5.3.1 Follow-up (Additional) Clinic Visit(s)

"Additional Clinic Visits" will be performed approximately 7 days after Ad hoc Clinic Visit. This is applicable for those subjects who received booster dose of rabies vaccine during Ad hoc Clinic Visit.

During the Additional Clinic Visit, the subject or legal guardian will be interviewed to determine if any AEs occurred and if any concomitant medications ***in conjunction to any SAEs*** or vaccines were taken/received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or AEs are present. AEs reported by the subject or legal guardian at this Additional Clinic Visit must be recorded in the subject's source document and if there is any SAE then it must be entered in Adverse Events CRF, as specified in section 7.1, Safety Assessment.

In order to investigate the prompt boostability of immune responses, 7 mL of blood sample will be drawn during ***A***dditional ***C***linic ***V***isit. The blood will be drawn only from those subjects who received booster dose of rabies vaccination during an Ad hoc Clinic Visit.

During Scheduled Clinic Visit and Additional Clinic Visit, subjects will be observed for at least 15 minutes after the blood draw for any AE. Record any such observation in the subject's source document only and not in the eCRF.

The site should schedule with the subject or legal guardian the next clinic visit.

The subject or legal guardian will receive a written reminder of the next planned study activity. The subject or legal guardian will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3.2 Safety Follow-up Calls

Not applicable.

5.4 Unscheduled Visits

An unscheduled visit describes a non-routine study visit triggered by a specific event. These could include anticipated or unanticipated AEs or interventions.

There are no anticipated specific symptoms or events for which any unscheduled visit is expected.

5.5 Study Termination Visit

The study termination visit will occur for all subjects on the Scheduled Clinic Visit 8 (Year 10). The date of termination is the date of the last contact (clinic visit) in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up or blood draw; it is the date consent is withdrawn. This date should be recorded on the termination CRF page. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see section 5.5.1, Early Termination Visit.

At the last clinic visit, the following procedures will be performed: blood sampling for immunogenicity, interview of subject or legal guardian to collect SAEs and the associated concomitant medications/vaccinations (if the subject received the booster dose during the last Ad hoc Clinic Visit).

The site will review with the subject or legal guardian the plan of when information relating to the subject's participation in the study may be available (e.g., study results). It will also be discussed how information relating to the subject's participation in the study

will be shared with the subject's healthcare provider, if the subject or legal guardian chooses to share this information.

The site will complete the termination CRF page and this will mark the completion of the subject's participation in the study.

5.5.1 Early Termination Visit

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor and, when possible, will perform the procedures listed below. The reason(s) for the early termination will be included in the subject's source documentation. If the Early Termination Visit is a telephone call, collect as much information as possible. Early Termination Visits include subjects who were enrolled but not treated.

At the clinic visit or during the telephone call, the following procedures will be performed, as applicable: interview of subject/legal guardian to collect AEs, concomitant medications/vaccinations, blood sampling for immunogenicity.

The site will review with the subject or legal guardian the plan of when information relating to the subject's participation in the study may be available (e.g., study results). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject or legal guardian chooses to share this information.

The site will complete the termination CRF page and this will mark the completion of the subject's participation in the study.

6.0 TREATMENT OF SUBJECTS

The vaccine associated with this study is to be stored separately from other vaccines and medications in a secure location under appropriate storage conditions with temperature monitoring.

All vaccines associated with this study must be checked for expiration date prior to use. Expired vaccines must not be administered to subjects.

6.1 Study Vaccine(s) (Amended 25 February 2019)

Rabipur®, purified chick-embryo cell derived (PCEC) rabies vaccine, GSK Vaccines GmbH (formerly Novartis Vaccines and Diagnostics GmbH), Marburg, Germany.

The vaccine presentation consists of powder (lyophilized vaccine) and solvent (water for injection) for solution for injection. For the composition of Rabipur® vaccine please refer to the SmPC supplied by GSK.

After reconstitution, a booster dose consists of 1.0 mL of PCEC rabies vaccine, containing rabies virus [inactivated strain Flury ***6.6*** Low Egg Passage (LEP)®] with a potency ≥2.5 IU/mL, and is to be administered via intramuscular (IM) injection.

The study vaccine should be stored in a secure and locked refrigerator at 2°C to 8°C.

The term ‘study vaccine’ refers to those vaccines provided by the Sponsor, which will be evaluated as part of the study objectives. The study vaccine specific to this study is Rabipur®, as described above.

6.2 Non-Study Vaccines

Not applicable.

6.3 Vaccine Preparation and Administration (Amended 25 February 2019)

The investigator or designee will be responsible for oversight of the administration of vaccine to subjects enrolled in the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

From the beginning of the study until 2018, vaccine assignment was randomly done by the study staff. From 2019 onwards, the SBIR system has been implemented for vaccine assignment to the subjects. The study staff will access the system and will enter

the subject identification number. The system will provide a treatment number for each subject.
When SBIR is not available, please refer to the SBIR user guide or the Supply and Cold Chain Guidance for specific instructions.

The study vaccine must be prepared according to the Rabipur® SmPC before use. Refer to the SmPC of Rabipur® in investigator site file. Note that the vaccine needs to be reconstituted before use. Expired vaccines must **NOT** be administered.

A single dose of 1.0 mL should be administrated ***intramuscularly*** in deltoid area ***of non-dominant arm*** by the designated and trained site staff. ***Subjects experiencing local AEs at the vaccination site could alternatively receive rabies vaccine in the deltoid muscle of the dominant arm.***

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

Prior to booster vaccination, subjects must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgment of the investigator to vaccinate.

Eligibility for booster vaccination is determined by following the inclusion and exclusion criteria outlined in section 4.0, and the criteria outlined in section 4.3, Criteria for Delay of Vaccination.

If, after having received a booster dose, the subject does not reach the adequate antibody concentration of 0.5 IU/mL at two consecutive determinations, neither at 7 days after the booster dose (i.e. Additional Clinic Visit) nor at the next yearly evaluation (i.e. Scheduled Clinic Visit), an additional booster dose may be administered at the following Ad hoc Clinic Visit. ***If the subject is still non-responder, subsequent management should be at the discretion of the investigator.***

Eligibility for non-study vaccines should be determined by the investigator, pending the review of the package insert of the relevant vaccine.

Study vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccine.

Standard immunization practices are to be observed and care should be taken to administer the injection intramuscularly. Before administering vaccine, the vaccination site is to be disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. **DO NOT inject intravascularly or intragluteal**y.

As with all injectable vaccines, trained medical personnel and appropriate medical treatment should be readily available in case of anaphylactic reactions following vaccine administration. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

6.4 Vaccine Administration Error or Overdose of Vaccine

Vaccine administration error is defined as receiving a dose of study vaccine that was not reconstituted as instructed or administered by a different route from the intended route of administration. An overdose of study vaccine (whether accidental or intentional) is defined when a dosage higher than the recommended booster dosage is administered.

Any vaccine administration error or overdose of study vaccine detailed in this protocol must be reported as an AE, and if the vaccine administration error or overdose is associated with a SAE, it must be reported as such within 24 hours to the Sponsor.

6.5 Prior and Concomitant Medications and Vaccines

All relevant prescription medications (e.g. immune suppressants, antimalarial drugs), vaccines and blood products taken or received by the subject between completion of V49_23 study and prior to the start of this extension study are to be recorded on the Prior and Concomitant Medications CRF.

In addition, the following are considered prior medications for this protocol: all medication/vaccines described in the inclusion and exclusion criteria of this protocol including:

- Receipt of rabies post exposure prophylaxis or booster dose of rabies vaccine following completion of V49_23 study.
- Rabies immunoglobulins.
- Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to informed consent.
- Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent.
- Immunoglobulins or any blood products within 180 days prior to informed consent.
- Currently receiving anti-malarial medications (e.g. Mefloquine).
- Any other vaccines within 28 days prior to the booster dose or planning to receive any vaccine within 28 days from the booster dose.

- Any investigational or non-registered medicinal product within 14 days before booster dose till next Scheduled Clinic Visit after booster dose administration.

The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source document and Concomitant Medications CRF. The use of antipyretics/analgesics within 24 hours prior to vaccine administration is a reason to delay study vaccination (see section 4.3, Criteria for Delay of Vaccination).

Medications taken for prophylaxis are those intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

Concomitant medications include all medications (including vaccines) taken by/administered to subjects who experienced SAEs during the safety follow up period after administration of the rabies vaccine booster dose, and must be documented on the Concomitant Medications CRF.

When recording concomitant medications/vaccines, they should be checked against the study entry and continuation criteria in section 4.0, Selection of Study Population to ensure that the subject should be enrolled/continue in the study.

6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor will ensure the following:

- Supply the study vaccine.
- Appropriate labeling of all study vaccines provided that complies with the legal requirements of each country where the study is to be performed.

The investigator must ensure the following:

- Acknowledge receipt of the study vaccines by a designated staff member at the site, including:

Confirmation that the vaccines were received in good condition

Confirmation to the Sponsor of the temperature range during shipment from the Sponsor to the investigator's designated storage location

- Proper storage of the study vaccines, including:

Storage in a secure, locked, temperature-controlled location.

Proper storage according to the instructions specified on the labels.

Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.

- Appropriate use of the study vaccines, including:

Use only in accordance with the approved protocol.

Proper handling, including confirmation that the vaccine has not expired prior to administration.

Appropriate documentation of administration of vaccines to study subjects including:

  - Date, dosage, batch/lot numbers, expiration dates, unique identifying numbers assigned to subjects and study vaccines, and time of vaccine administration. This information will be maintained in an accountability log that will be reviewed by the site monitor.
  - Reconciliation of all vaccines received from the Sponsor. Reconciliation is defined as maintaining records of which and how many vaccines were received, which vaccines were administered to subjects, which vaccines were destroyed ***locally***, and which vaccines were returned to the Sponsor ***or depot***, as applicable.

- Proper adherence to the local institutional policy with respect to destruction of study vaccines.
- Complete record keeping of vaccine use, wastage, return or destruction, including documentation of:

Copy of the site's procedure for destruction of hazardous material.

Number of doses destroyed, date of destruction, destruction code (if available), method of destruction, and name of individual performing destruction.

In the event that the use cannot be authorized, the Sponsor will make every effort to replace the vaccine supply. All vaccines used in conjunction with this protocol must be stored separately from normal hospital/practice stocks to prevent unintentional use of study vaccines outside of the clinical study setting.

Monitoring of vaccine accountability will be performed by the study monitor during site visits and at the completion of the study.

At the conclusion of the study, and as appropriate during the course of the study, the investigator must ensure that all unused study vaccines, packaging and supplementary labels are destroyed ***either*** locally (upon approval from Sponsor) or returned to the Sponsor ***or depot, as applicable***.

7.0 ASSESSMENTS (Amended 25 February 2019)

7.1 Safety Assessment

The measures of safety used in this study are ***based on comparable*** routine clinical procedures. They include a close vigilance for, and stringent reporting of SAEs following booster vaccination.

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

7.1.1 Solicited Adverse Events

No solicited local or systemic AEs or other solicited adverse events are intended to be collected in this study.

Solicited Local Adverse Events

No solicited local adverse events are intended to be collected in this study.

Solicited Systemic Adverse Events

No solicited systemic adverse events are intended to be collected in this study.

Other Solicited Adverse Events

There are no other solicited adverse events intended to be collected in this study.

7.1.2 Unsolicited Adverse Events

An unsolicited adverse event is an AE that was not solicited and that was spontaneously communicated by a subject or legal guardian who has signed the informed consent. In this study only SAEs and the associated concomitant medications following PCEC rabies booster vaccinations ***will be collected***, starting from the time ***the subject receives the booster dose until completion of safety follow up period, which is, the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier (see section 7.1.4, Serious Adverse Events and section 7.1.5,***

Methods for Recording Adverse Events and Serious Adverse Events), based on the subject's interview during Clinic Visit. SAEs collected during physical exams at Scheduled and Ad hoc visits will be as well collected.

7.1.3 Evaluation of Adverse Events

During Scheduled Clinic Visit and Additional Clinic Visit, subjects will be observed for at least 15 minutes after the blood draw for any AE. Record any such observation in the subject's source document only and not in the eCRF.

7.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in one or more of the following:

- Death.
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Required or prolonged hospitalization.
- Persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions).
- 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 subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as non-serious.

It should be noted that a serious adverse event need not, by definition, be severe.

In this study only SAEs and the associated concomitant medications following PCEC rabies booster vaccinations will be collected (see section 7.1.5, Methods for Recording Adverse Events and Serious Adverse Events).

The period of observation for SAEs extends from the time the subject receives the booster dose until completion of safety follow-up period (the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier).

7.1.4.1 Adverse Events of Special Interest

Adverse events of special interest (AESIs) are not assessed during the study.

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

All findings in subjects experiencing SAEs and any medication or other therapeutic measures used to treat the SAE in addition to the outcome of the SAE after PCEC rabies booster dose or collected during physical exams at Scheduled and Ad hoc visits, must be reported both on the VSAE Report Form which is part of the Investigator Site File and in the eCRF.

Investigator must report those events to his/her corresponding EC or applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the Sponsor. During the course of the study, all SAEs which occur from the time of booster administration until completion of safety follow-up period (the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier), whether considered to be associated with the study vaccination or not, must be reported within 24 hours of the site becoming aware of the event to GSK or its designee. Specific instructions and contact details for collecting and reporting SAEs to GSK will be provided to the investigator.

After receipt of the initial report, representatives of GSK or its designee will contact the investigator if it is necessary to obtain further information for assessment of the event.

GSK or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse vaccine reactions (also known as SUSARs) to the regulatory authorities and the IRB/EC. If a SUSAR or other safety signal relating to use of one of the study vaccines is reported to GSK or its designee, the Sponsor will communicate the information to the investigator and the investigator will be responsible for submitting this information to the EC and other relevant authorities.

All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. SAEs that are judged to be possibly or probably related to the study vaccine should be reported to the Sponsor as related/suspected events***, irrespectively of time frame of SAEs reporting.***

The relationship of the study vaccine to a SAE will be determined by the investigator based on the following definitions:

1. Related/suspected

The SAE is judged by the investigator to be possibly or probably related to the study vaccine on the AE CRF page (see section 7.1.3, Evaluation of Adverse Events).

2. Not Related

The SAE is not related if exposure to the study vaccine has not occurred, **or** the occurrence of the SAE is not reasonably related in time, **or** the SAE is considered unlikely to be related to use of the study vaccine, i.e., there are no facts (evidence) or arguments to suggest a causal relationship.

In addition, SAEs will be evaluated by the Sponsor or designee for "expectedness." An unexpected AE is one that is not listed in the current SmPC or an event that is by nature more specific or more severe than a listed event.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the Medical History CRF.
If the onset of an event occurred before the subject entered the study (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious.
If the investigator ***judges that the*** hospitalization was prolonged as a result of ***the event itself*** or was necessary due to a worsening of the pre-existing condition, ***the hospitalization would then be considered as a SAE.***

Additionally, the investigator will evaluate whether the SAEs lead to withdrawal of subject from the study.

All SAEs will be monitored until resolution or until the investigator assesses them as chronic or stable. All subjects experiencing SAEs from the time the subject receives the booster dose until he or she completes the specified safety follow-up period (i.e. the day of next Scheduled Clinic Visit after booster vaccination ***or on the date of Early Termination Visit, whichever is earlier***) - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. The investigator's assessment of ongoing SAEs at the time of each subject's last visit should be documented in the subject's source document.

7.1.5.1 Post-Study Events

Any SAE that occurs outside of the protocol-specified ***safety*** follow-up period (***after Study Termination Visit or Early Termination Visit whichever is earlier***) and ***the investigator considers*** to be caused by the study vaccine must be reported to GSK or its designee.

7.1.6 Pregnancies

To ensure subjects' safety, ***all*** pregnanc***ies*** must be reported to GSK or delegate ***within 2 weeks of site becoming aware of a pregnancy***. If the subject agrees to submit this information, the pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of safety follow-up for the study has ended.

Pregnancy data must be recorded on a Pregnancy Report CRF (initial report) and Pregnancy Follow-Up CRF (outcome report) and reported to GSK or delegate. Instructions and contact details for submitting the Pregnancy CRFs will be provided to the investigator.

Any pregnancy outcome meeting the definition of SAEs (see section 7.1.4, Serious Adverse Events) reported in subjects who received booster administration needs to be reported within 24 hours of the site becoming aware of the event to GSK or delegate using the VSAE Report Form and be recorded in the CRF(s).
The Pregnancy Form must also be updated for further internal processing.

Any pregnancy outcome meeting the definition of SAEs reported in subjects who have NOT received booster administration need to be reported within 24 hours of the site becoming aware of the event to GSK or delegate using the VSAE Report Form, although such SAEs will not be a part of the Clinical database and do not need to be recorded in the CRF(s).
The Pregnancy Form must also be updated for further internal processing.

7.1.7 Safety Laboratory Measurements

This study has no safety laboratory measurements.

7.2 Efficacy Assessment

This study has no efficacy measurements.

7.3 Immunogenicity Assessment

The measures of immunogenicity used in this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response).

- Protection against rabies is dependent on the presence of RVNA. WHO recommended method to measure RVNA serum concentrations is RFFIT. A neutralizing antibody titer of ≥0.5 IU/mL is regarded by the WHO as being an 'adequate' antibody response following rabies vaccination, and is used as a threshold in clinical trials.
- Blood samples from all subjects at Scheduled Clinic Visits 1 through 8 (Year 3 through Year 10), and, only from those subjects who received booster vaccination, also at Additional Clinic Visits 1.2 through 7.2, will be used for serology analysis. Refer to section 3.0, Study Design.
- Testing will be conducted by a GSK or designated, qualified laboratory in a blinded manner towards the treatment arm. Refer to the Protocol Ancillary Document for names and details.

8.0 STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Primary Endpoint(s)

8.1.1.1 Primary Safety Endpoint(s) (Amended 25 February 2019)

For subjects receiving PCEC rabies booster vaccination, SAEs and the associated concomitant medications will be collected starting from the time of booster administration until ***completion of safety follow-up period (the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier).***

8.1.1.2 Primary Efficacy Endpoint(s)

Not applicable.

8.1.1.3 Primary Immunogenicity Endpoint(s) (Amended 25 February 2019)

- Time to first RVNA concentrations <0.5 IU/mL.
- ***Geometric Mean Antibody Concentrations (***GMCs***)*** and ***Geometric Mean ratio (***GMRs***)*** for subjects receiving the booster dose, as measured by antibody concentration at 7 days after the booster dose vs. antibody concentration before the booster dose.
- Percentages of subjects with RVNA concentrations ≥0.5 IU/mL, as measured by RFFIT assay at 7 days after the booster dose and at Year 3, 4, 5, 6, 7, 8, 9 and 10 Scheduled Clinic Visits.

8.1.2 Secondary Endpoint(s)

8.1.2.1 Secondary Safety Endpoint(s)

Not applicable.

8.1.2.2 Secondary Efficacy Endpoint(s)

Not applicable.

8.1.2.3 Secondary Immunogenicity Endpoint(s) (Amended 25 February 2019)

- GMCs at Year 3, 4, 5, 6, 7, 8, 9 and 10;

- Reverse Cumulative Distribution Plots (RCDPs) at Year 3, 4, 5, 6, 7, 8, 9 and 10;
- Percentages of subjects with RVNA concentrations ≥0.5 IU/mL, as measured by RFFIT assay at Year 3, 4, 5, 6, 7, 8, 9 and 10.

8.1.3 Exploratory Endpoint(s)

8.1.3.1 Exploratory Safety Endpoint(s)

Not applicable.

8.1.3.2 Exploratory Efficacy Endpoint(s)

Not applicable.

8.1.3.3 Exploratory Immunogenicity Endpoint(s)

Not applicable.

8.2 Success Criteria

8.2.1 Success Criteria for Primary Objective(s)

Not applicable.

8.2.1.1 Success Criteria for Primary Safety Objective(s)

Not applicable.

8.2.1.2 Success Criteria for Primary Efficacy Objective(s)

Not applicable.

8.2.1.3 Success Criteria for Primary Immunogenicity Objective(s)

Not applicable.

8.2.2 Success Criteria for Secondary Objective(s)

8.2.2.1 Success Criteria for Secondary Safety Objective(s)

Not applicable.

8.2.2.2 Success Criteria for Secondary Efficacy Objective(s)

Not applicable.

8.2.2.3 Success Criteria for Secondary Immunogenicity Objective(s)

Not applicable.

8.3 Analysis Sets

8.3.1 All Enrolled Set

All screened subjects who provide informed consent and provide demographic and/or baseline screening assessments.

8.3.2 All Exposed Set

All subjects in the enrolled set who receive a booster dose.

8.3.3 Safety Set

Safety Set

All subjects in the Exposed Set with unsolicited adverse event data.

Overall Safety Set

Not applicable.

8.3.4 Full Analysis Set (FAS) Immunogenicity Set

Full Analysis Set Immunogenicity

Time to first RVNA concentrations <0.5 IU/mL.

All subjects in the All Enrolled Set who provide immunogenicity data until first time RVNA concentration is <0.5 IU/mL.

GMR for subjects receiving the booster dose, as measured by antibody concentration at 7 days after the booster dose vs. antibody concentration before the booster dose.

All subjects in the All Enrolled Set who provide immunogenicity data after booster dose.

Percentages of subjects with RVNA concentrations ≥0.5 IU/mL, as measured by RFFIT assay at 7 days after the booster dose and at Year 3, 4, 5, 6, 7, 8, 9 and 10 Scheduled Clinic Visits.

All subjects in the All Enrolled Set who provide immunogenicity data after booster dose.

GMCs, percentages and RCDPs of subjects with RVNA concentrations ≥0.5 IU/mL, as measured by RFFIT assay at Year 3, 4, 5, 6, 7, 8, 9 and 10.

All subjects in the All Enrolled Set who provide immunogenicity data at relative time-points. After having received the booster dose, subjects will not be included in these analyses any longer.

Further details on Full Analysis Immunogenicity sets are provided in the statistical analysis plan.

8.3.5 Per Protocol (PP) Set Immunogenicity Set

All subjects in the FAS Immunogenicity who:

- Correctly receive the booster dose (only for analysis of boostability).
- Have no protocol deviations leading to exclusion (see section 8.3.8, Protocol Deviations) as defined prior to analysis.
- Are not excluded due to other reasons defined prior to analysis (see section 8.3.8, Protocol Deviations)

Examples for subjects excluded due to other reasons than protocol deviations are:

Subjects who withdrew informed consent.

Analogously to FAS, inclusion of subjects in the PPS is defined by objective.

Further details on Per Protocol Immunogenicity sets are provided in the statistical analysis plan.

8.3.6 Other Analysis Sets

Not applicable.

8.3.7 Subgroups

Not applicable.

8.3.8 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. CSR-reportable protocol deviations will be defined as exclusionary from the analysis according to protocol objectives and endpoints, which will be specified in the statistical analysis plan. In some cases exclusion of data may be due to a reason other than a protocol deviation, e.g. early termination.

8.4 Statistical Analysis Plan

8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height and weight, body mass index (BMI) at enrolment will be calculated overall and by vaccine group.

Distributions of subjects by sex and ethnic origin will be summarized overall and by vaccine group.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective

Number and percentages of SAEs will be summarized only for subjects receiving a booster dose by the vaccination regimen received in the parent study V49_23 and overall.

8.4.2.1.1 Analysis of Extent of Exposure

Not applicable.

8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

Not applicable.

8.4.2.1.3 Analysis of Unsolicited Adverse Events (Amended 25 February 2019)

This analysis applies to all ***SAEs*** occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of booster dose. SAE starting prior to booster dose will not be recorded. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA

dictionary. The serious adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

All reported serious adverse events, as well as serious adverse events judged by the investigator as at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. When a serious adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be produced for the following categories:

- Serious adverse events.
- Serious adverse events that are possibly or probably related to vaccine.
- Serious Adverse event leading to withdrawal.
- Deaths

Data listings of all serious adverse events will be provided by subject. In addition, serious adverse events in the categories above will be provided as listed data.

8.4.2.1.4 Analysis of Safety Laboratory Values

Not applicable.

8.4.2.2 Analysis of Primary Efficacy Objective(s)

Not applicable.

8.4.2.2.1 Statistical Hypotheses

Not applicable.

8.4.2.2.2 Analysis Sets

Not applicable.

8.4.2.2.3 Statistical Methods

Not applicable.

8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

8.4.2.3.1 Statistical Hypotheses

Not applicable.

8.4.2.3.2 Analysis Sets (Amended 25 February 2019)

All Enrolled Set.

FAS-1: Booster Immunogenicity Analysis Set.

Analyses on PPS will be conducted only if more than 10% of subjects have CSR-reportable ***protocol*** deviations (by objective).

For analysis sets definition see section 8.3.

8.4.2.3.3 Statistical Methods (Amended 25 February 2019)

Time to first RVNA concentrations <0.5 IU/mL.

For each subject time to first RVNA concentrations <0.5 IU/mL will be calculated. Kaplan-Meier ***(KM)*** estimate of the survival function, along with 95% CIs, will be estimated and displayed per each vaccination regimen. Standard errors of the KM estimates will be based on the Greenwood's method; 25th and 75th percentile and median survival will be provided if estimable.

In this setting, the event/failure will be represented by the administration of the booster dose. Subjects without event will be regarded as right-censored data. Dropouts will be considered as non-informative data and judged as Missing Completely At Random (MCAR) as an association between the missingness mechanism and the vaccine efficacy or safety is implausible.

Group comparisons for first occurrences of a boost will be performed using the unadjusted Cox proportional hazard regression model (only treatment effect will be included). Ties will be handled with the exact method as it assumes that there is a true but unknown ordering for the tied event times. Hazard ***Ratios*** (HR) and 95% CIs will be computed. In case of not estimable HRs, alternative methods will be attempted.

It is expected that no or very few subjects will need more than one booster dose during the study conduct. Nevertheless, a contingency analysis will be performed counting the frequency of subjects who receive 0 booster, 1 booster, 2 boosters, 3 or more boosters.

If a relevant number of subjects will need more than one booster dose during the study conduct, the Andersen-Gill method will be used to analyze multiple events data.

Geometric Mean Ratio (GMR).

RVNA GMCs will be based on the logarithmically transformed (base10) values.

For subjects receiving a booster dose, analysis of boostability will be conducted 7 days and at also approximately 6 months after administration of the booster dose by providing GMRs and associated 95% CIs, considering the antibody value at the booster visit as baseline (denominator) and the antibody concentration at 7 days (and approximately at 6 months) after booster as the numerator.

Additionally, all boosted subjects will be pooled together and their RVNA concentrations analyzed using an ANOVA model that includes vaccine regimen group and time in study of the booster dose as factors in the model along with their interaction. For this analysis, values, as measured at day 7 (and also approximately at 6 months) after booster dose, will be used.

Percentages of subjects with RVNA concentrations ≥ 0.5 IU/mL, as measured by RFFIT assay at 7 days after the booster dose and at subsequent scheduled clinical visit.

Percentages and 95% CIs will be presented by vaccine regimen.

8.4.3 Analysis of Secondary Objective(s)

Not applicable.

8.4.3.1 Analysis of Secondary Safety Objective(s)

8.4.3.1.1 Analysis of Extent of Exposure

Not applicable.

8.4.3.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

Not applicable.

8.4.3.1.3 Analysis of Unsolicited Adverse Events

Not applicable.

8.4.3.1.4 Statistical Hypotheses

Not applicable.

8.4.3.1.5 Analysis Sets

Not applicable.

8.4.3.1.6 Statistical Methods

Not applicable.

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

8.4.3.2.1 Statistical Hypotheses

Not applicable.

8.4.3.2.2 Analysis Sets

Not applicable.

8.4.3.2.3 Statistical Methods

Not applicable.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

8.4.3.3.1 Statistical Hypotheses

Not applicable.

8.4.3.3.2 Analysis Sets

FAS-2: Long term Immunogenicity Analysis Set.

8.4.3.3.3 Statistical Methods

Geometric Mean Concentration (GMC).

RVNA GMCs will be based on the logarithmically transformed (base10) values.

GMCs with the associated 95% confidence intervals (CIs) will be computed for each vaccine group at Year 3, 4, 5, 6, 7, 8, 9 and 10 by taking the exponential of the corresponding log-transformed (least squares) means and 95% confidence intervals, from an ANOVA model with fixed factors for group and center. Group differences along with

95%CIs will also be computed. Subjects will be included in this analysis until they receive the booster dose and they will be excluded thereafter.

Reverse Cumulative Distribution Plots.

The reverse cumulative distribution plots will be provided at Year 3, 4, 5, 6, 7, 8, 9 and 10 by treatment group.

Percentages of subjects with RVNA concentrations ≥ 0.5 IU/mL.

As a form of supplementary information, also percentage of subjects with RVNA concentrations ≥0.5 IU/mL, as measured by RFFIT assay at Year 3, 4, 5, 6, 7, 8, 9 and 10 will be presented in a tabular fashion.

8.4.4 Analysis of Exploratory Objectives

Not applicable.

8.4.4.1 Analysis of Exploratory Safety Objective(s)

Not applicable.

8.4.4.2 Analysis of Exploratory Efficacy Objective(s)

Not applicable.

8.4.4.3 Analysis of Exploratory Immunogenicity Objective(s)

Not applicable.

8.5 Sample Size and Power Considerations of Primary Objectives

Not applicable.

8.6 Interim Analyses

In order to understand complete evolution of the antibody decay over time and the effect of the booster dose, every year, an immunogenicity and safety analysis will be carried out and the results will be stored in the internal clinical data repository.

Two Clinical Study Reports (CSR) are planned:

- One interim CSR will be released after all subjects will complete Scheduled Clinic Visit 4 (i.e. Year 6). This CSR will include both immunogenicity and safety analyses

halfway through study. The interim CSR might be submitted to the Health Authority in case results support indication for the booster dose at a given time after the primary regimen.

- The final CSR will be released at the completion of the study and will include all study data from Visit 1 (Year 3) to Visit 8 (Year 10).

For the interim and final CSR a full database lock will be required. For the other yearly analyses, a protected snapshot will be performed.

9.0 SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

In order to ensure consistency across sites, study monitoring and auditing will be standardized and performed in accordance with the Sponsor's or delegated contract research organization's (CRO) standard operating procedures and applicable regulatory requirements (e.g., FDA, EMA, and ICH guidelines).

Prior to enrolment of the first study subject, GSK or delegate will train investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices and all electronic systems. CRFs supplied by the Sponsor must be completed for each enrolled subject (see section 8.3.1, All Enrolled Set for definition of enrolled subject). Documentation of screened but not enrolled subjects must be maintained at the site and made available for review by the site monitor. Data and documents will be checked by the Sponsor and/or monitor.

9.1 Source Documentation

Prior to the start of the study, the site staff participating in the study conduct will be instructed on what documents will be required for review as source documents. The kinds of documents that will serve as source documents will be agreed between Sponsor or delegate and investigator and designees and specified in the Source Data Agreement prior to subject enrolment.

In addition, source documentation **must** include all of the following: subject identification (on each page), eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of adverse events, documentation of prior/concomitant medication/vaccines, study vaccine receipt/dispensing/return records, study vaccine administration information, any data collected by a telephone conversation with the subject or legal guardian and date of completion and reason.

The subject or legal guardian must also allow access to the subject's medical records. Each subject or legal guardian must be informed of this prior to the start of the study and consent for access to medical records may be required in accordance with local regulations.

All safety data reported by subjects must be written down in source documents prior to entry of the data into CRFs. If there are multiple sources of information (e.g., verbal report of the subject, telephone contact details, medical chart) supporting the diagnosis of an adverse event, these sources must be identified in the source documents, discrepancies between sources clarified, the ultimate diagnosis must be justified and written in the source documents, and this diagnosis must be captured in the Adverse Event CRF (AE

CRF). The AE CRF must also capture which source(s) of information were used to determine the adverse event (e.g., subject recall, medical chart).

9.2 Study Monitoring, Auditing and Source Data Verification

Prior to enrolment of the first study subject, GSK or its designee (e.g., a CRO) will develop a Clinical Monitoring Plan to specify how centralized and/or on-site monitoring, including clinical specimens reconciliation, will be performed for the study. Study progress will be monitored by GSK or its designee as frequently as necessary to ensure:

- that the rights and well-being of human subjects are protected,
- the reported study data are accurate, complete, and verifiable from the source documents and
- the conduct of the study is in compliance with the current approved protocol/amendment(s), GCP and applicable regulatory requirements.

Contact details for the GSK team or its designee involved in study monitoring will be provided to the investigator. Study data recorded on CRFs will be verified by checking the CRF entries against source documents in order to ensure data completeness and accuracy as required by study protocol

Data verification may also be performed through a centralized review of data (e.g., checking for outliers or other anomalies). Additional documents such as the investigator site file, pharmacy records, and informed consent documentation must also be available for review if requested. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

The investigator and/or site staff must make source documents of subjects enrolled in this study available for inspection by GSK or its representative at the time of each monitoring visit and Sponsor audits, when applicable. These documents must also be available for inspection, verification and copying, as required by regulations, by officials of the regulatory health authorities (e.g., FDA, European Medicines Agency and others) and/or ECs/IRBs. The investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

10.0 DATA MANAGEMENT

10.1 Data Entry and Management (Amended 25 February 2019)

In this study, all clinical data (including, but not limited to, SAEs, concomitant medications, medical history, and physical assessments), and immunogenicity data will be entered onto CRFs in a timely fashion by the investigator and/or the investigator's dedicated site staff. Data entered onto CRFs are stored on a secure website. The data collected on this secure website are assimilated into an EDC system, which is compliant with Title 21 Part 11 policies of the Code of Federal Regulations (FDA 1997). The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the CRFs to verify their accuracy.

Access to the EDC system for data entry or review will require training and distinct individual access code assignments to those site staff members who will be entering study data and those involved in study oversight who may review study data. Data are collected within the EDC system, to which the Sponsor and site monitors have exclusively "read only" access.

10.2 Data Clarification

As part of the conduct of the trial, the Sponsor may have questions about the data entered by the site, referred to as queries. The monitors and the Sponsor are the only parties that can generate a query. All corrections and clarifications will be entered into the EDC system and will be identified by the person entering the information, the reason for the change, as well as the time of the changes made. If changes are made to a previously and electronically signed CRF, the investigator must confirm and endorse the changes.

10.3 Data Protection

GSK respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

The Sponsor as Data Controller according to the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data (95/46/EC) confirms herewith compliance to Directive 95/46/EC in all stages of Data Management.

11.0 RECORD RETENTION

Investigators must retain all study records required by GSK and by the applicable regulations in a secure and safe facility. The investigator must consult a GSK representative before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Essential documents must be retained for 15 years. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable national regulatory or institutional requirements.

These principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing.

12.0 USE OF INFORMATION AND PUBLICATION

GSK assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov, and in compliance with current regulations.

GSK also assures that key results of this clinical study will be posted in a publicly accessible database within the required time-frame from the end of study as defined in section 3.9, End of Study.

In accordance with standard editorial, ethical practices and current guidelines of Good Publication Practice (Graf 2009), GSK will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement prior to the start of the study. The coordinating investigator will also sign the clinical study report on behalf of the principal investigators (CPMP/EWP/2747/00). Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of GSK personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate GSK personnel.

GSK must be notified of any intent to publish data collected from the study and prior approval from GSK must be obtained prior to submission for publication.

13.0 ETHICAL CONSIDERATIONS

13.1 Regulatory and Ethical Compliance

The study will be conducted in compliance with the protocol, GCP and applicable regulatory requirement(s).

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations: including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare, GSK codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Council 2001, US Code of Federal Regulations, ICH 1997).

13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written informed consent, as described in section 5.1.1, Informed Consent. Before the start of the study, the investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB/EC. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject or the designee. The subject/designee must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent process may be conducted prior to any study related procedure on Day 1. If the subject is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature.

Prior to the start of the study, GSK will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by GSK before submission to the IRB/EC and a copy of the approved version must be provided to the GSK monitor after IRB/EC approval.

Women of childbearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements indicated in the protocol for at least 6 months after the booster vaccination.

If case of doubts on the ability of a subject to adhere to these requirements, that subject should not be allowed in the study

13.3 Responsibilities of the Investigator and IRB/EC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Properly constituted IRB/EC is defined in ICH Guideline for Good Clinical Practice E6 (R1), Section 3 (ICH 1997). A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to GSK before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to GSK monitors, auditors, GSK Clinical Quality Assurance representatives, designated agents of GSK, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform GSK immediately that this request has been made.

The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.
- Demonstrating the capability of recruiting the required number of suitable subjects within the recruitment period.
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period.
- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions
- Ensuring that appropriately trained health care professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any adverse event related to the study.
- If permission to do so is given by the subject, ensuring that the subject's primary healthcare provider is informed of the subject's participation in the study.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone

number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) to the IRB/IEC for review and approval/favourable opinion,

(b) to the Sponsor for agreement and, if required,

(c) to the regulatory authority(ies).

13.4 Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by GSK, health authorities where required, and the IRB/EC. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/EC approval. Notwithstanding, the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, GSK should be notified of this action, the IRB/EC at the study site, and, if required by local regulations, the relevant health authority should be informed within 10 working days.

14.0 REFERENCE LIST

Code of Federal Regulations (1997): Food and Drug Administration, U.S. Department of Health and Human Services: Title 21, Part 11: Electronic Records Electronic Signatures. Federal Register 62: 13464

European Parliament (1995): Directive 95/46/EC of the European Parliament and of the Council of 4 April 2001. Official Journal of the European Communities. L 281/31-39

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GlaxoSmithKline Biologicals	
Vaccine Value & Health Science (VVHS)	
Protocol Amendment 2	
eTrack study number and Abbreviated Title	205214 [RABIES (V49)-018 BST 017 - V49_23E1]
Amendment number:	Amendment 2
Amendment date:	25 February 2019
Co-ordinating author:	PPD Scientific Writer

Rationale/background for changes:

- Clarification of the timeframe between each yearly Scheduled Visit: Visit 1 date has to be used as reference for calculating next visit date (e.g. Visit 1: 31 JAN 15, then Visit 2: 31 JAN 16 ± 28 days, Visit 3: 31 JAN 17 ± 28 days) *(Table 2a)*.

- Clarification of the time window between the Scheduled Clinic Visit and the Ad hoc Visit: the previous wording was not clear enough, team agreed to precise that booster administration at the Ad hoc Visit should happen between 6 to 9 months after the Scheduled Clinic Visit (*Table 2b*).

- Clarification that physical exams have to be done by practitioners in accordance with their institutional policy (*Table 2a and 2b, Section 5.1.2 Screening).* It has been specified that collection of vital signs must be done during all Ad hoc Visits prior booster administration. During the other visits (Scheduled and Additional), they could be measured at the discretion of the investigator (*Section 5.1.2 Screening*).

- Clarification on the number of additional booster doses a subject may receive: if, after a first booster dose, the adequate RVNA level is not reached at two consecutive determinations, a subject may receive an additional booster. If he/she is still a non-responder, the investigator should manage at its discretion. (*Synopsis*; *Section 3.1 Overview of Study Design; Section 5.2 Ad hoc Clinic Visits; Section 6.3 Vaccine Preparation and Administration*).

- Clarification on premature withdrawal from the study: there was no mention on the

procedure to follow in case a subject misses the Ad hoc Visit and the possible booster dose. This has been added to the relevant section, specifying that in this case the subject could come to the next following Scheduled Visit and having a blood draw according to protocol. In case RVNA concentrations <0.5 IU/mL, a booster may be given. (*Section 3.8 Premature Withdrawal from Study*).

- Clarification on Exclusion Criteria: prior to Scheduled Visit criteria have been added, as they were not previously detailed (only criteria prior to study entry and booster vaccination were stated).
  Some clarification to the criteria to be checked prior the Ad hoc Visit has been added: if a subject received corticosteroids, antineoplastic and immunomodulating agents or radiotherapy within 90 days prior the Ad hoc Visit (and not prior to informed consent as previously stated) or receipt or planning to receive them during the participation to the study, they have to be withdrawn. Subjects should be excluded if they received any non-study rabies vaccine (*Section 4.2 Exclusion Criteria)*.

- Clarification on assignment of the Subject ID: this is a unique ID number and is the same as the one attributed during the parental study V49_23 (*Section 5.1.2 Screening*). It has been specified that since current year, 2019, a centralized Randomization System on internet (SBIR) has been implemented for treatment allocation. The study staff need to access the system and to enter the subject identification number for obtaining a treatment number for each subject (footnote e in *Table 2b; Section 5.1.4 Randomization; Section 6.3 Vaccine Preparation and Administration*).

- Update the name of the document used for identification of the health care practitioners to Study Staff Delegation of Responsibilities (SS DoR) (*Section 5.1.2 Screening*).

- Global rewording of *Section 7 Assessment* for simplification and clarification of the text.

- To clarify that ONLY SAEs (and the associated concomitant medications) experienced by subjects who received the rabies booster and those collected during Physical examinations must be reported period (Tables *2a* and *2b; Section 3.4.1 Data Collected from Subjects; Section 7.1.4 Serious Adverse Events*).
  Clarification of period of collection: for those subjects, SAEs and the associated concomitant medications will be collected starting from the time of booster administration until the completion of safety follow-up period (Study design and

Safety Endpoint in *Synopsis*; footnote b in *Table 2a*; *Section 3.1 Overview of Study Design*; *Section 7 Assessment*; *Section 7.1.4 Serious Adverse Events*; *Section 8.1.1.1 Primary Safety Endpoints; Section 5.3.1 Follow-up Clinic Visit*). Safety follow-up period is defined as the day of the next Scheduled Clinic Visit after booster vaccination or the date of Early Termination Visit, whichever is earlier.

- To clarify the procedures for reporting AEs:
  - SAEs (and any medication or other therapeutic measures used to treat the AE) will be recorded in the eCRF as well as in the VSAE form.
  - Any AEs (e.g. after blood draw) will be recorded ONLY in the source documents (*Section 3.4.2 Tools Used for Data Collection; Section 7.1.5 Methods for Recording Adverse Events and Serious Adverse Events).*

- Rewording of the paragraph related to the recording of pre-existing event or condition that results in hospitalization for clarification purpose *(Section 7.1.5 Methods for Recording Adverse Events and Serious Adverse Events).*

- Clarification for post-study events collection: all SAEs that occur outside the protocol-specified safety follow-up period and that the investigator considers to be caused by the study vaccine must be reported to GSK or its designee (*Section 7.1.5.1 Post-Study Events).*

- Specification on vaccine preparation and administration: vaccine has to be administered intramuscularly in the deltoid area of the non-dominant arm. Alternatively, it can be administered in the deltoid area of the dominant arm if subjects experience local AEs on primary vaccination site (*Section 6.3 Vaccine Preparation and Administration*).

- Clarification on vaccine tracking at the conclusion of the study: all unused supply vaccine and supplementary labels are destroyed either locally (upon approval from Sponsor) or returned to the Sponsor or depot, as applicable (*Section 3.8 Premature Withdrawal from Study - Administrative reason; Section 6.6 Vaccine Supply, Labeling, Storage and Tracking*). Authorization for use (AFU) wording has been removed throughout the protocol as it is no longer used (*Section 6.6 Vaccine Supply, Labeling, Storage and Tracking*).

- To clarify the reporting of pregnancies:
  - Any pregnancy outcome meeting the definition of a SAE reported in subjects who received booster administration needs to be reported within 24

hours of the site becoming aware of the event to GSK or delegate using the VSAE Report Form and be recorded in the CRF(s). The Pregnancy Form must also be updated for further internal processing.
- Any pregnancy outcome meeting the definition of SAEs reported in subjects who have NOT received booster administration need to be reported within 24 hours of the site becoming aware of the event to GSK or delegate using the VSAE Report Form, although such SAEs will not be a part of the Clinical database and do not need to be recorded in the CRF(s). The Pregnancy Form must also be updated for further internal processing. (*Section 7.1.6 Pregnancies).*

- To correct some typographical errors.

- To update the *List of Abbreviations* and acronyms throughout the text.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

SYNOPSIS

Study design and Safety Endpoint

For subjects receiving PCEC rabies booster vaccination, Serious Adverse Events (SAEs) and the associated concomitant medications will be collected starting from the time of booster administration ~~and~~ until ~~the day of next Scheduled Clinic Visit~~ ***completion of safety follow-up period (the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier)***.

Study Population and Subject Characteristics

Inclusion criteria: Subjects who sign***ed*** the informed consent prior to the study entry,

Ad hoc Clinic Visits

The booster dose will be given in an "Ad hoc Clinic Visit***"*** which is planned to occur as soon as the results of the antibody assay will be available and within approximately 6 ***to 9*** months from the blood draw taken during a previous "Scheduled Clinic Visit".

Additional Clinic Visit

If, after having received a booster dose, the subject does not reach the adequate antibody concentration (i.e., RVNA ≥0.5IU/mL) at two consecutive determinations, neither at 7 days after the booster dose (i.e. Additional Clinic Visit) nor at the next yearly evaluation (i.e., Scheduled Clinic Visit), an additional booster dose may be administered at the following Ad hoc Clinic Visit. ***If the subject is still non-responder, subsequent management should be at the discretion of the investigator.***

Should a subject have RVNA concentrations below 0.5 IU/mL at blood draw performed at the final Scheduled Clinic Visit (Year 10), ~~the subject will be invited~~ the ***investigator will invite the*** subject to receive a booster dose of the rabies vaccine outside the study following standard clinical practice and there will be no further analyses performed on this additional vaccination.

Statistical Analyses

For subjects receiving a booster dose, analysis of boostability will be conducted 7 days (and also approximately 6 ***to 9*** months) after administration of the booster dose by providing GMRs and associated 95% CIs, considering the antibody value at the booster visit as baseline (denominator) and the antibody concentration at 7 days (and also approximately ~~at~~ ***between*** 6 ***to 9*** months) after booster as the numerator.

TABLE 2a Scheduled Clinic Visits: For All Subjects

Visit Type		Scheduled Clinic Visit							Final Scheduled Clinic Visit
Study Period		**Day 1 Year 3**	**Year 4**	**Year 5**	**Year 6**	**Year 7**	**Year 8**	**Year 9**	**Year 10**
Visit Window (Days)*		**n/a**	**-28 to +28**	**-28 to +28**	**-28 to +28**	**-28 to +28**	**-28 to +28**	**-28 to +28**	**-28 to +28**
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Event	**References**								
Screening and Safety									
Informed Consent [a]	Section 5.1.1	X							
Medical History	Section 5.1.2	X	X	X	X	X	X	X	X
Physical Exam[d]	Section 5.1.2	X	X	X	X	X	X	X	X
Exclusion/Inclusion Criteria	Section 4.0	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	Sections 5.1.2 and 6.5	X							
Assess SAEs and Relevant ***Concomitant*** Medications [b]	Sections 7.1.4, 5.1.2 and 6.5		X	X	X	X	X	X	X
Observe for at Least 15 Minutes Post Blood Draw and Assess AEs (if any)	Section 7.1.3	X	X	X	X	X	X	X	X
Immunogenicity									
Serology Blood Draw	Section 3.5	X	X	X	X	X	X	X	X
Study Completion Procedures									
Study Termination [c]	Section 5.5								X

[a] Confirm consent form signed prior to any procedures.

[b] SAEs and the associated concomitant medications will be collected ONLY from those subjects who will receive booster vaccine during ~~last~~ ***the*** Ad hoc Clinic Visit, ~~SAEs and the associated concomitant medications will be collected starting from the booster administration and until the day of next Scheduled Clinic Visit.~~ ***starting from the time of booster administration until completion of safety follow-up period (the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier).***

[c] Subjects who terminate the study early are recommended to complete certain study-related procedures. See section 5.5 for further details.

[d] ***Physical exams have to be done by practitioners in accordance with their institutional policy. Should the physical assessment reveal any abnormal values or events, which fall under definition of SAE, these must be documented in the CRF Adverse Events Form and reported to sponsor.***

****Visit 1 date to be used as reference for calculating next visit date (e.g. V1: 31 JAN 15, V2: 31 JAN 16 ± 28 days, V3: 31 JAN 17 ± 28 days).***

TABLE 2b Ad hoc and Additional Clinic Visit

Visit Type		**Clinic Visit**													
		Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]
Study Period		Year 3, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 1	Year 3, 7 days after Ad hoc Clinic Visit 1.1	Year 4, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 2	Year 4, 7 days after Ad hoc Clinic Visit 2.1	Year 5, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 3	Year 5, 7 days after Ad hoc Clinic Visit 3.1	Year 6, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 4	Year 6, 7 days after Ad hoc Clinic Visit 4.1	Year 7, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 5	Year 7, 7 days after Ad hoc Clinic Visit 5.1	Year 8, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 6	Year 8, 7 days after Ad hoc Clinic Visit 6.1	Year 9, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 7	Year 9, 7 days after Ad hoc Clinic Visit 7.1
Visit Window (Days)		**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**
Visit Number		**1.1**	**1.2**	**2.1**	**2.2**	**3.1**	**3.2**	**4.1**	**4.2**	**5.1**	**5.2**	**6.1**	**6.2**	**7.1**	**7.2**
Study Event	**References**														
Medical History[c]	Section 5.1.2	X		X		X		X		X		X		X	

Visit Type		Clinic Visit													
		Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]
Study Period		Year 3, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 1	Year 3, 7 days after Ad hoc Clinic Visit 1.1	Year 4, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 2	Year 4, 7 days after Ad hoc Clinic Visit 2.1	Year 5, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 3	Year 5, 7 days after Ad hoc Clinic Visit 3.1	Year 6, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 4	Year 6, 7 days after Ad hoc Clinic Visit 4.1	Year 7, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 5	Year 7, 7 days after Ad hoc Clinic Visit 5.1	Year 8, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 6	Year 8, 7 days after Ad hoc Clinic Visit 6.1	Year 9, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 7	Year 9, 7 days after Ad hoc Clinic Visit 7.1
Visit Window (Days)		**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**
Visit Number		**1.1**	**1.2**	**2.1**	**2.2**	**3.1**	**3.2**	**4.1**	**4.2**	**5.1**	**5.2**	**6.1**	**6.2**	**7.1**	**7.2**
Study Event	**References**														
Physical Exam[c]	Sections 5.1.2 and 5.2	X		X		X		X		X		X		X	
Pregnancy Test[c, d]	Sections 3.5 and 5.1.2	X		X		X		X		X		X		X	
Verification of Relevant Exclusion/Inclusion Criteria[c]	Section 4.0	X		X		X		X		X		X		X	
Vaccination[e]	Section 5.2	X		X		X		X		X		X		X	
30 Minutes Post Booster Injection Assessment	Section 5.2.1	X		X		X		X		X		X		X	

Visit Type		Clinic Visit													
		Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]
Study Period		Year 3, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 1	Year 3, 7 days after Ad hoc Clinic Visit 1.1	Year 4, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 2	Year 4, 7 days after Ad hoc Clinic Visit 2.1	Year 5, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 3	Year 5, 7 days after Ad hoc Clinic Visit 3.1	Year 6, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 4	Year 6, 7 days after Ad hoc Clinic Visit 4.1	Year 7, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 5	Year 7, 7 days after Ad hoc Clinic Visit 5.1	Year 8, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 6	Year 8, 7 days after Ad hoc Clinic Visit 6.1	Year 9, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 7	Year 9, 7 days after Ad hoc Clinic Visit 7.1
Visit Window (Days)		**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**
Visit Number		**1.1**	**1.2**	**2.1**	**2.2**	**3.1**	**3.2**	**4.1**	**4.2**	**5.1**	**5.2**	**6.1**	**6.2**	**7.1**	**7.2**
Study Event	**References**														
Assess SAEs and Relevant ***Concomitant*** Medications[f]	Sections 7.1.4, 5.1.2 and 6.5	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity															
Serology Blood Draw	Section 3.5		X		X		X		X		X		X		X
Observe for at Least15 Minutes Post Blood Draw and Assess AEs (if any)	Section 7.1.3		X		X		X		X		X		X		X

Visit Type		Clinic Visit													
		Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]
Study Period		Year 3, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 1	Year 3, 7 days after Ad hoc Clinic Visit 1.1	Year 4, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 2	Year 4, 7 days after Ad hoc Clinic Visit 2.1	Year 5, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 3	Year 5, 7 days after Ad hoc Clinic Visit 3.1	Year 6, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 4	Year 6, 7 days after Ad hoc Clinic Visit 4.1	Year 7, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 5	Year 7, 7 days after Ad hoc Clinic Visit 5.1	Year 8, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 6	Year 8, 7 days after Ad hoc Clinic Visit 6.1	Year 9, ~~approx.~~ ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 7	Year 9, 7 days after Ad hoc Clinic Visit 7.1
Visit Window (Days)		**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**	**n/a**	**-1 to +1**
Visit Number		**1.1**	**1.2**	**2.1**	**2.2**	**3.1**	**3.2**	**4.1**	**4.2**	**5.1**	**5.2**	**6.1**	**6.2**	**7.1**	**7.2**
Study Event	**References**														

[e] Ad hoc Clinic Visit (which is planned to occur as soon as the results of the antibody assay will be available and within approximately 6 months from the blood draw taken during a previous "Scheduled Clinic Visit") is only applicable for those subjects with RVNA concentrations <0.5 IU/mL during this extension study. See sections 3.1 and 3.9 for further details.

[f] Additional Clinic Visit (within approximately 7 days from Ad hoc Clinic Visit) only applicable for subjects who will receive a booster dose of PCEC rabies vaccine during Ad hoc Clinic Visit.

[g] Procedure to be performed prior to vaccination. ***Physical exams have to be done by practitioners in accordance with their institutional policy. Should the physical assessment reveal any abnormal values or events, which fall under definition of SAE, these must be documented in the CRF Adverse Events Form and reported to sponsor.***

[h] Only for female subject of childbearing potential who are eligible to receive the booster dose.

[i] ***GSK Biologicals' Randomization System on Internet (SBIR) will be used for Treatment allocation.***

[j] SAEs and the associated concomitant medications will be collected starting from the booster administration ~~and~~ until ~~the day of next Scheduled Clinic Visit.~~ ***completion of safety follow-up period (the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier)***.

LIST OF ABBREVIATIONS

AE	Adverse ***E*** ~~e~~vent
eCRF	***electronic*** Case Report Form
HR	***Hazard Ratios***
ICH	International Conference ~~on~~ ***for*** Harmonisation of Technical Requirements for ~~Registration of~~ Pharmaceuticals for Human Use
KM	***Kaplan-Meier***
mg	***Milligram***
SBIR	***Source DataBase for Internet Randomization***
SmPC	***Summary of Product Characteristics***

1.0 BACKGROUND AND RATIONALE

1.1 Background

The incubation period in humans is usually several weeks to months, but ranges from <1 week to >1 year (***World Health Organization [***WHO***]*** 2013).

More than 60,000 people die of rabies every year and 95% of these deaths occur in Asia and Africa (~~World Health Organization [~~WHO~~]~~ 2013).

Pre-exposure prophylaxis is recommended for anyone who is at continual, frequent or increased risk for exposure to the rabies virus, as a result of ~~their~~ ***her/his*** residence or occupation, including travelers in high-risk areas (WHO 2013).

Protection against rabies is dependent on the presence of ~~r~~***R***abies ~~v~~***V***irus ~~n~~***N***eutralizing ~~a~~***A***ntibodies (RVNA).

Rabipur® is a ~~p~~***P***urified ~~c~~***C***hick-~~e~~***E***mbryo ~~c~~***C***ell ~~c~~***C***ulture (PCEC) rabies vaccine indicated for active immunization against rabies in individuals of all ages.

Although in clinical trials persistence of adequate antibody concentrations for 2 years after immunisation with Rabipur® without additional booster has been observed in 100% of subjects, and experience shows that Rabipur® booster doses are generally required every 2-5 years following the conventional PrEP regimen, as recommended by WHO and following current Rabipur® ~~SmPC~~ ***Summary of Product Characteristics (SmPC)***,

3.0 STUDY DESIGN

3.1 Overview of Study Design

Subjects who were randomized into one of the 3 rabies vaccination group regimen***s***,

All sites will be trained in a uniform fashion and th~~at~~***ose*** sites will be monitored to ensure consistency in study execution across all centers.

Vaccination procedures:

If, after having received a booster dose, the subject does not reach the adequate antibody concentration of 0.5 IU/mL at two consecutive determinations, neither at 7 days after the booster dose (i.e. Additional Clinic Visit) nor at the next yearly evaluation (i.e. Scheduled Clinic Visit), an additional booster dose may be administered at the following Ad hoc Clinic Visit. ***If the subject is still non-responder, subsequent management should be at the discretion of the investigator.***

Should a subject have RVNA concentrations below 0.5 IU/mL at blood draw performed at the final Scheduled Clinic Visit (Year 10), the ~~subject will be invited~~ ***investigator will invite the subject*** to receive a booster dose of the rabies vaccine outside the study following standard clinical practice and there will be no further analyses performed on this additional vaccination.

Post-vaccination evaluations:

- Starting from the time of booster administration ~~and~~ until ~~the day of next Scheduled Clinic Visit:~~ ***completion of safety follow-up period (the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier)*** SAEs and the associated concomitant medications will be recorded by interviewing the subject during next ~~c~~***C***linic ~~v~~***V***isit and based on the subject's medical records.

(e.g. booster administration at the Ad hoc Clinic Visit 1.1 for subjects with RVNA concentrations ***<0.5 IU/mL at the Scheduled Clinic Visit 1***).

3.4.1 Data Collected from Subjects

The following data will be collected from each subject over the duration of their study participation:

- Demographic Information.
- Medical History.
- Concomitant Medications ***(only when associated to a SAE).***

3.4.2 Tools Used for Data Collection

Data will be recorded in the subject's source record and collected on ~~electronic Case Report Forms (~~eCRFs~~)~~.

Any safety information either within 30 minutes of post vaccination and/or up to the day of next Scheduled Clinic Visit ***and which can be considered an AE*** must be recorded in subject's source document and it must be described as a verbally reported adverse event.

Any AE ***that occurs during the specified safety collection period*** which fulfils any of the seriousness criteria mentioned in section 7.1.4 must be reported to the sponsor ***via the Vaccines Serious Adverse Event (VSAE) Form which is part of the Investigator Site File*** and therefore entered on the Adverse Event CRF.

Any adverse event that is considered to be caused by the study vaccine and occurs outside the protocol-specified follow-up period should be reported to the sponsor (section 7.1.5.1, Post-study events).

3.8 Premature Withdrawal from Study

Lost to Follow-Up: For subjects who fail to show up for final ***Scheduled*** ~~e~~***C***linic ~~v~~***V***isit, or for three consecutive Scheduled Clinic Visits, study staff are encouraged to make at least three documented attempts to contact the subject by telephone and at least one documented written attempt to contact the subject or legal guardian to encourage the completion of study termination procedures. ***In case an Ad hoc Visit is missed, the subject could come to the next following Scheduled Visit and having a blood draw according to protocol. In case RVNA concentrations <0.5 IU/mL, a booster may be given according to protocol.***

Administrative Reason: If the clinical study is prematurely terminated by the Sponsor, the investigator is to promptly inform the study subjects and local ~~EC/IRB~~ ***IRB/EC (Institutional Review Board/ Ethic Committee)*** and should assure appropriate therapy and follow up for the subjects. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/vaccines, etc.) must be ***destroyed either locally or*** returned to the Sponsor ***or depot, as applicable.***

4.0 SELECTION OF STUDY POPULATION

4.2 Exclusion Criteria

***Prior to Scheduled Visit*, each subject must not have:**

7. ***History of exposure to suspected or confirmed rabid animal.***
8. ***Receipt of rabies immunoglobulins, non-study rabies vaccine following completion of V49_23 study.***
9. ***Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.***
10. ***Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.***
11. ***Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to informed consent or planning to receive them during the participation to the study.***
12. ***Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent or planning to receive them during the participation to the study.***
13. ***Received immunoglobulins or any blood products within 180 days prior to informed consent or planning to receive them during the participation to the study.***
14. ***Study personnel as well as their immediate family or household member.***
15. ***Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.***

Prior to booster vaccination, each subject eligible for booster vaccination should be in good health status and must not have none of the following:

2. Abnormal function of the immune system resulting from:
    a. Clinical conditions.
    b. Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior ~~to informed consent~~ ***the Ad hoc visit*** or receipt or planning to receive them during the participation to the study.
    c. Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior ~~to informed consent~~ ***the Ad hoc visit*** or receipt or planning to receive them during the participation to the study.
3. ***Receipt of non-study rabies vaccine.***
4. ~~3.~~ Receipt of any other vaccines within 28 days prior to the booster dose or planning to receive any vaccine within 28 days from the booster dose.
5. ~~4.~~ Receipt of any investigational or non-registered medicinal product within 14 days

before booster dose till next Scheduled Clinic Visit after booster dose administration.

6. ~~5.~~ Receipt of anti-malarial medications (e.g. Mefloquine) within 14 days before booster dose till next Scheduled Clinic Visit after booster dose administration.

5.0 STUDY PROCEDURES

The sections that follow provide an overview of the procedures that ***have*** ~~are~~ to be followed in enrolling, evaluating, and following subjects who participate in this clinical study.

5.1.2 Screening

After an individual has consented to participate in the study and informed consent is signed, that individual ~~will be given a unique Screening Number manually created by the investigator.~~ ***will be assigned a unique Subject ID which she/he is carrying from V49_23 study (the parent study)***.

Collect***ion of*** vital signs~~:~~ (heart rate, respiratory rate, blood pressure, and temperature) ***has to be done during all Ad hoc Visits prior booster administration. At Scheduled and Additional Visits, their measurement should be at the discretion of the investigator.***

A general physical examination is to be performed by a qualified health care practitioner~~.~~***, in accordance with their institutional policy.*** "Qualified health care practitioner" refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the ~~Study Staff Signature Log~~ ***Study Staff Delegation of Responsabilities (SSDoR)***.

5.1.3 Enrollment

After signing the informed consent form, if an individual is determined to be eligible for study participation, the investigator will enroll the subject into the EDC ***(Electronic Data Capture)*** system.

5.1.4 Randomization

Subject numbers (ID) will be pre-loaded into a centralized Randomization System on internet (SBIR).

5.2 Ad Hoc Clinic Visit(s) - Vaccination Clinic Visit(s)

The first dose of booster vaccination with rabies vaccine will be performed in a clinical visit occurring as soon as the results of the antibody assay will be available and within approximately 6 ***to 9*** months.

Only for those subjects with RVNA concentrations <0.5 IU/mL at the first visit of this extension study (Day 1, Year 3) or at the following yearly visits (Year 4 to Year 9) a booster dose of PCEC rabies vaccine will be administered during the next planned Ad ~~H~~***h***oc Clinic Visit.

Should the subject be a low responder to a booster dose of the rabies vaccine provided during this extension study and not achieve adequate antibody concentrations following a booster injection neither at 7 days (following the blood drawn at the "Additional Clinic Visits" after the booster) nor at the next evaluation (following the blood drawn at the "Scheduled Clinic Visits" after the booster), a subsequent booster dose may be administered at the subsequent "Ad hoc Clinic Visit". ***If the subject is still non-responder, subsequent management should be at the discretion of the investigator.***

5.3.1 Follow-up (Additional) Clinic Visit(s)

During the Additional Clinic Visit, the subject or legal guardian will be interviewed to determine if any AEs occurred and if any concomitant medications ***in conjunction to any SAEs*** or vaccines were taken/received in the time since the last clinic visit.

In order to investigate the prompt boostability of immune responses, 7 mL of blood sample will be drawn during ~~a~~***A***dditional ~~c~~***C***linic ~~v~~***V***isit

6.0 TREATMENT OF SUBJECTS

6.1 Study Vaccine(s)

After reconstitution, a booster dose consists of 1.0 mL of PCEC rabies vaccine, containing rabies virus [inactivated strain Flury ***6.6*** Low Egg Passage (LEP)®] with a potency ≥2.5 IU/mL, and is to be administered via intramuscular (IM) injection.

6.3 Vaccine Preparation and Administration

From the beginning of the study until 2018, vaccine assignment was randomly done by the study staff. From 2019 onwards, the SBIR system has been implemented for vaccine assignment to the subjects. The study staff will access the system and will enter

the subject identification number. The system will provide a treatment number for each subject.
When SBIR is not available, please refer to the SBIR user guide or the Supply and Cold Chain Guidance for specific instructions.

A single dose of 1.0 mL should be administrated ***intramuscularly*** in deltoid area ***of non-dominant arm*** by the designated and trained site staff. ***Subjects experiencing local AEs at the vaccination site could alternatively receive rabies vaccine in the deltoid muscle of the dominant arm.***

If, after having received a booster dose, the subject does not reach the adequate antibody concentration of 0.5 IU/mL at two consecutive determinations, neither at 7 days after the booster dose (i.e. Additional Clinic Visit) nor at the next yearly evaluation (i.e. Scheduled Clinic Visit), an additional booster dose may be administered at the following Ad hoc Clinic Visit. ***If the subject is still non-responder, subsequent management should be at the discretion of the investigator.***

6.6 Vaccine Supply, Labeling, Storage and Tracking

Reconciliation of all vaccines received from the Sponsor. Reconciliation is defined as maintaining records of which and how many vaccines were received, which vaccines were administered to subjects, which vaccines were destroyed ~~at the site~~ ***locally***, and which vaccines were returned to the Sponsor ***or depot***, as applicable.

At the conclusion of the study, and as appropriate during the course of the study, the investigator must ensure that all unused study vaccines, packaging and supplementary labels are destroyed ***either*** locally (upon approval from Sponsor) or returned to the Sponsor ***or depot, as applicable***.

~~Confirmation by the Sponsor that the vaccines are authorized for use.~~

~~Not use of vaccines prior to receipt of authorization for use from the Sponsor.~~

~~Vaccines that have been stored differently from the manufacturer's indications **must not** be used unless the Sponsor provides written authorization for use.~~

7.0 ASSESSMENTS

7.1 Safety Assessment

The measures of safety used in this study are ***based on comparable*** routine clinical procedures. They include a close vigilance for, and stringent reporting of SAEs following booster vaccination.

7.1.2 Unsolicited Adverse Events

An unsolicited adverse event is an AE that was not solicited and that was spontaneously communicated by a subject or legal guardian who has signed the informed consent. In this study only SAEs and the associated concomitant medications following PCEC rabies booster vaccinations ***will be collected***, starting from the time ~~of booster administration and until the day of next Scheduled Clinic Visit, will be collected in the AE and concomitant medications eCRF pages~~. ***the subject receives the booster dose until completion of safety follow up period, which is, the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier (see sections 7.1.4 Serious Adverse Events and 7.1.5 Methods for Recording Adverse Events and Serious Adverse Events), based on the subject's interview during Clinic Visit. SAEs collected during physical exams at Scheduled and Ad hoc visits will be as well collected.***

7.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in one or more of the following:

- Death.
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Required or prolonged hospitalization.
- Persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions).
- 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 subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as non-serious.

It should be noted that a serious adverse event need not, by definition, be severe.

~~Serious adverse events will be captured both on the Vaccines Serious Adverse Event (VSAE) form as well as on the AE CRF. All SAEs will be evaluated by the investigator~~

~~for relationship of the event to study vaccine. SAEs that are judged to be possibly or probably related to the study vaccine should be reported to the Sponsor as related/suspected events.~~
~~The relationship of the study treatment to an SAE will be determined by the investigator based on the following definitions:~~
~~1. Related/suspected~~
~~The SAE is judged by the investigator to be possibly or probably related to the study vaccine on the AE CRF page (see section 7.1.3, Evaluation of Adverse Events).~~
~~2. Not Related~~
~~The SAE is not related if exposure to the study vaccine has not occurred, or the occurrence of the SAE is not reasonably related in time, or the SAE is considered unlikely to be related to use of the study vaccine, i.e., there are no facts (evidence) or arguments to suggest a causal relationship.~~
~~The relationship of the study vaccine to an SAE will be determined by the investigator.~~
~~In addition, SAEs will be evaluated by the Sponsor or designee for "expectedness." An unexpected AE is one that is not listed in the current Summary of Product Characteristics or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.~~
~~In addition, a pre-existing event or condition that results in hospitalization should be recorded on the Medical History CRF. If the onset of an event occurred before the subject entered the study (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical study or was necessary due to a worsening of the pre-existing condition.~~
~~Additionally, the investigator will evaluate whether the SAEs lead to withdrawal of subject from the study.~~
~~All SAEs will be monitored until resolution or until the investigator assesses them as chronic or stable. All subjects experiencing SAEs from the time the subject receives the booster dose until he or she completes the specified safety follow-up period (i.e. the day of next Scheduled Clinic Visit after booster vaccination) - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. The investigator's assessment of ongoing SAEs at the time of each subject's last visit should be documented in the subject's source document.~~

In this study only SAEs and the associated concomitant medications following PCEC rabies booster vaccinations will be collected (see section 7.1.5 Methods for Recording Adverse Events and Serious Adverse Events).

The period of observation for SAEs extends from the time the subject receives the booster dose until completion of safety follow-up period (the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier).

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

~~Findings regarding Serious Adverse Events must be reported on an Adverse Events CRF, and on the VSAE form, which is part of the Investigator Site File. All findings in subjects experiencing AEs must be reported also in the subject's source document.~~

~~During the course of the study, all SAEs which occur from the time of booster administration and until the day of next Scheduled Clinic Visit , whether considered to be associated with the study vaccination or not, must be reported~~ **~~within 24 hours of the site becoming aware of the event~~** ~~to GSK or its designee. Specific instructions and contact details for collecting and reporting SAEs to GSK will be provided to the investigator.~~

~~All SAEs after PCEC rabies booster dose are also to be documented on the Adverse Events CRF. Any medication or other therapeutic measures used to treat the AE will be recorded on the appropriate CRF(s) in addition to the outcome of the SAE.~~

~~After receipt of the initial report, representatives of GSK or its designee will contact the investigator if it is necessary to obtain further information for assessment of the event.~~

~~All SAEs after PCEC rabies booster dose must be reported by the investigator to his/her corresponding EC or applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the Sponsor.~~

~~GSK or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse vaccine reactions (also known as SUSARs) to the regulatory authorities and the IRB/EC. If a SUSAR or other safety signal relating to use of one of the study vaccines is reported to GSK or its designee, the Sponsor will communicate the information to the investigator and the investigator will be responsible for submitting this information to the EC and other relevant authorities.~~

All findings in subjects experiencing SAEs and any medication or other therapeutic measures used to treat the SAE in addition to the outcome of the SAE after PCEC rabies booster dose or collected during physical exams at Scheduled and Ad hoc visits, must be reported both on the VSAE Report Form which is part of the Investigator Site File and in the eCRF.

Investigator must report those events to his/her corresponding EC or applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the Sponsor. During the course of the study, all SAEs which occur from the time of booster administration until completion of safety follow-up period (the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier), whether considered to be associated with the study vaccination or not, must be reported within 24 hours of the site becoming aware of the event to GSK or its designee. Specific instructions and contact details for collecting and reporting SAEs to GSK will be provided to the investigator.

After receipt of the initial report, representatives of GSK or its designee will contact the investigator if it is necessary to obtain further information for assessment of the event.

GSK or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse vaccine reactions (also known as SUSARs) to the regulatory authorities and the IRB/EC. If a SUSAR or other safety signal relating to use of one of the study vaccines is reported to GSK or its designee, the Sponsor will communicate the information to the investigator and the investigator will be responsible for submitting this information to the EC and other relevant authorities.

All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. SAEs that are judged to be possibly or probably related to the study vaccine should be reported to the Sponsor as related/suspected events***, irrespectively of time frame of SAEs reporting.***

The relationship of the study vaccine to a SAE will be determined by the investigator based on the following definitions:

1. Related/suspected

The SAE is judged by the investigator to be possibly or probably related to the study vaccine on the AE CRF page (see section 7.1.3, Evaluation of Adverse Events).

2. Not Related

The SAE is not related if exposure to the study vaccine has not occurred, **or** the occurrence of the SAE is not reasonably related in time, **or** the SAE is considered unlikely to be related to use of the study vaccine, i.e., there are no facts (evidence) or arguments to suggest a causal relationship.

In addition, SAEs will be evaluated by the Sponsor or designee for "expectedness." An unexpected AE is one that is not listed in the current SmPC or an event that is by nature more specific or more severe than a listed event.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the Medical History CRF.
If the onset of an event occurred before the subject entered the study (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious.
If the investigator ***judges that the*** hospitalization was prolonged as a result of ***the event itself*** or was necessary due to a worsening of the pre-existing condition, ***the hospitalization would then be considered as a SAE.***

Additionally, the investigator will evaluate whether the SAEs lead to withdrawal of subject from the study.

All SAEs will be monitored until resolution or until the investigator assesses them as chronic or stable. All subjects experiencing SAEs from the time the subject receives the booster dose until he or she completes the specified safety follow-up period (i.e. the day of next Scheduled Clinic Visit after booster vaccination ***or on the date of Early Termination Visit, whichever is earlier***) - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. The investigator's assessment of ongoing SAEs at the time of each subject's last visit should be documented in the subject's source document.

7.1.5.1 Post-Study Events

Any SAE that occurs outside of the protocol-specified ***safety*** follow-up period ~~(from the time of booster administration and until the day of next Scheduled Clinic Visit)~~ (***after Study Termination Visit or Early Termination Visit whichever is earlier***) and ***the investigator*** consider~~ed~~ to be caused by the study vaccine must be reported to GSK or its designee ~~as spontaneous reporting.~~

7.1.6 Pregnancies

To ensure subjects' safety, ***all*** pregnanc***ies*** must be reported to GSK or delegate ***within 2 weeks of site becoming aware of a pregnancy***. If the subject agrees to submit this information, the pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of

any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of safety follow-up for the study has ended.

Pregnancy data must be recorded on a Pregnancy Report CRF (initial report) and Pregnancy Follow-Up CRF (outcome report) and reported to GSK or delegate. Instructions and contact details for submitting the Pregnancy CRFs will be provided to the investigator.

Any pregnancy outcome meeting the definition of SAEs (see section 7.1.4, Serious Adverse Events) reported in subjects who received booster administration needs to be reported within 24 hours of the site becoming aware of the event to GSK or delegate using the VSAE Report Form and be recorded in the CRF(s).
The Pregnancy Form must also be updated for further internal processing.

Any pregnancy outcome meeting the definition of SAEs reported in subjects who have NOT received booster administration need to be reported within 24 hours of the site becoming aware of the event to GSK or delegate using the VSAE Report Form, although such SAEs will not be a part of the Clinical database and do not need to be recorded in the CRF(s).
The Pregnancy Form must also be updated for further internal processing.

8.0 STATISTICAL CONSIDERATIONS

8.1.1.1 Primary Safety Endpoint(s)

For subjects receiving PCEC rabies booster vaccination, SAEs and the associated concomitant medications will be collected starting from the time of booster administration ~~and~~ until ~~the day of next Scheduled Clinic Visit.~~ ***completion of safety follow-up period (the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier).***

8.1.1.3 Primary Immunogenicity Endpoint(s)

~~GMCs and GMRs~~ ***Geometric Mean Antibody Concentrations (***GMCs***)*** and ***Geometric Mean ratio (***GMRs***)*** for subjects receiving the booster dose.

8.1.2.3 Secondary Immunogenicity Endpoint(s)

~~Geometric Mean Antibody Concentrations (~~GMCs~~)~~ at Year 3, 4, 5, 6, 7, 8, 9 and 10

8.4.2.1.3 Analysis of Unsolicited Adverse Events

This analysis applies to all ~~serious adverse events~~ ***SAEs***

8.4.2.3.2 Analysis Sets

Analyses on PPS will be conducted only if more than 10% of subjects have CSR-reportable ***protocol*** deviations (by objective).

8.4.2.3.3 Statistical Methods

Kaplan-Meier ***(KM)***
Hazard ~~r~~***Ratios*** (HR)

10.0 DATA MANAGEMENT

10.1 Data Entry and Management

and immunogenicity data will be entered onto ~~case report forms (~~CRFs~~)~~ in a timely fashion by the investigator and/or the investigator's dedicated site staff. Data entered onto CRFs are stored on a secure website. The data collected on this secure website are assimilated into an ~~electronic data capture (~~EDC~~)~~