BLA Clinical Review Memorandum

Application Type	Supplemental BLA (sBLA)
STN	103931/5342
CBER Received Date	September 9, 2024
PDUFA Goal Date	July 24, 2025
Division / Office	DCTR/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Nana Aburjania, MD
Review Completion Date / Stamped Date	July 24, 2025
Supervisory Concurrence	Meghan Ferris, MD, MPH Andrea Hulse, MD
Applicant	Sanofi Pasteur
Established Name	Rabies vaccine
(Proposed) Trade Name	Imovax Rabies
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Lyophilized and reconstituted, with each 1.0 mL dose containing a minimum of 2.5 international units of rabies antigen
Dosage Form(s) and Route(s) of Administration	Administered intramuscularly as a 1.0 mL dose
Dosing Regimen	Dosing regimen depends on nature or risk of exposure, rabies immune status, and immune competence of the patient
Indication(s) and Intended Population(s)	Indicated for pre- and post-exposure prophylaxis against rabies in all age groups
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
CNS	central nervous system
CSR	Clinical Study Report
D	day
FAS	Full Analysis Set
FASI	Full Analysis Set for immunogenicity
GCP	Good Clinical Practice
GMT	geometric mean titer
HRIG	Human Rabies Immune globulin
ICF	informed consent form
ID	intradermally
IM	intramuscularly
IND	Investigational New Drug
IU/mL	international units per milliliter
LAR	legally authorized representative
LL	lower limit
LLOQ	lower limit of quantification
LMP	last menstrual period
NI	noninferiority
PeRC	Pediatric Review Committee
PPAS	Per-Protocol Analysis Set
PEP	post-exposure prophylaxis
PI	prescribing information
PrEP	pre-exposure prophylaxis
RFFIT	Rapid Fluorescent Focus Inhibition Test
RIG	rabies immune globulin
RVNA	rabies virus neutralizing antibody
SAE	serious adverse event
SafAS	Safety Analysis Set
SAP	Statistical Analysis Plan
sBLA	supplemental Biologics License Application
SCR	seroconversion rate
sPEP	simulated post-exposure prophylaxis
USPI	United States Prescribing Information
V	visit
VRVg-2	Purified Vero Rabies Vaccine - Serum Free
WHO	World Health Organization
WRO	Written Response Only
Y	year

1. EXECUTIVE SUMMARY

Human rabies is an acute, progressive encephalomyelitis that is nearly always fatal once symptoms begin. Human death from rabies can be effectively prevented through vaccination. Post-exposure prophylaxis (PEP) is key in prevention, which includes a series of human rabies vaccine doses, often with human rabies immunoglobulin (if indicated), and wound washing at the exposure site. In addition, persons with higher risk of exposure to rabies virus are recommended to receive preexposure prophylaxis (PrEP), a series of human rabies vaccine doses administered before an exposure occurs. The objective of PrEP is to eliminate the need for administering rabies immune globulin (RIG) and to prime the immune system so that it generates a rapid immune response to a booster vaccination in the event of a future exposure to rabies (Briggs 2021).

Imovax Rabies, a rabies vaccine manufactured by Sanofi, is indicated for PrEP and PEP against rabies. Imovax Rabies is approved for use in the United States (U.S.) for all age groups. In accordance with the current (October 2019) prescribing information (PI), Imovax Rabies is indicated as a 3-dose PrEP regimen against rabies. This regimen consists of one intramuscular (IM) injection given on Days 0, 7, and either 21 or 28. However, current clinical practice in the U.S. differs from the Imovax Rabies PI. Instead, it follows the U.S. Advisory Committee on Immunization Practices (ACIP) recommendations. In 2021-2022, ACIP revised the PrEP regimen, reducing the number of doses from 3 to 2, administered on Days 0 and 7 in all persons for whom rabies PrEP is indicated. Sanofi submitted a supplemental BLA (sBLA) for Imovax Rabies to add a 2-dose PrEP regimen to the U.S. Prescribing Information (USPI) to align with ACIP recommendations.

The Applicant submitted data from two clinical trials in support of a 2-dose Imovax Rabies PrEP regimen:

- VAJ00001: A Phase III, open-label, randomized, active-controlled multi-center study in participants ≥ 2 years of age conducted in the Philippines.
- VRV12: A Phase III, observer-blind, randomized, active-controlled, multi-center study in participants ≥ 1 years of age conducted in Thailand.

Study VAJ00001 was not conducted under a U.S. Investigational New Drug (IND) application.

- The primary objective of this study was to demonstrate that a shorter (1-week, 2-dose) Imovax Rabies IM PrEP regimen was noninferior (NI) to the reference (3-week, 3-dose) Imovax Rabies IM PrEP regimen. The NI hypothesis was based on evaluation of the 2-sided 95% confidence interval (CI) of the difference in percentages of participants with a rabies virus neutralizing antibody (RVNA) titer of ≥0.5 IU/mL 14 days after the last PrEP vaccination. NI would be demonstrated if the lower limit (LL) of the 95% CI of the difference of the 2 percentages was > -5%.
- A key secondary objective was to describe in each group the RVNA titers at baseline and at 14 days after the last Imovax Rabies vaccination when administered as a PrEP regimen.

The presence of RVNA in serum is considered a reliable postvaccination indicator of active immunization against rabies. The Rapid Fluorescent Focus Inhibition Test (RFFIT), is a cell-based assay used to measure RVNA in serum samples, helping determine the level of protection against rabies in humans and animals. The World Health Organization (WHO) recommends an antibody level of 0.5 IU/mL as being evidence of an adequate immune response after vaccination.

Studies have demonstrated protection at 0.1 IU/mL in cats and 0.2 IU/mL in dogs; consequently, 0.5 IU/mL is a conservative RVNA threshold to account for inherent variability in antibody measurement by various virus neutralization methods (WHO 2017). Prior to 2021/2022, the ACIP considered complete neutralization of rabies virus to occur at a 1:5 dilution by RFFIT (roughly correlating to a titer of 0.1 – 0.3 IU/mL) (Rao 2022).

Study VAJ00001 did not meet its pre-defined NI endpoint. One hypothesis offered by the Sponsor for why the study failed to meet the NI endpoint is that the immunogenicity assessment was performed too soon at D21, (D14 post last dose) versus the standard timeframe of 21 - 28 days post last dose to allow for a peak immune response (WHO 2017). However, the study was not designed to assess additional timepoints; therefore, the definitive cause of the narrowly missed primary endpoint remains unknown.

In Study VAJ00001, simulated post-exposure prophylactic (sPEP) doses were administered to confirm that participants who received a 2-dose PrEP regimen had an appropriate anamnestic immune response upon revaccination. In Study VAJ00001,100% of participants developed a robust immune response post sPEP dosing administered one year after the initial PrEP vaccination series, as measured by RVNA titers. The universal response to sPEP among participants demonstrates that PrEP was effective in priming participants to induce a robust anamnestic immune response, hence achieving its purpose, regardless of the priming dosing regimen received.

Given these considerations, and the fact that Study VAJ00001 narrowly missed the NI margin, we requested that the Applicant submit additional effectiveness data to support the 2-dose PrEP regimen using appropriate timepoints for immunogenicity assessments.

Subsequently, the Applicant added a 5th secondary immunogenicity objective to the already ongoing Study VRV12. This objective compared immune responses generated by the 2-dose Imovax Rabies vaccine regimen with those generated by the 3-dose regimen (Cohort 1, Group 3). The immunogenicity assessment after two doses were administered was scheduled at D28 in Study VRV12 (21 days after the 2nd dose). Data generated from Study VRV12 met its pre-defined NI criterion (percentage of participants achieving an RVNA titer ≥0.5 IU/mL after 2-dose Imovax Rabies at D28 was NI to 3-dose Imovax Rabies at D42), supporting that the 2-dose PrEP regimen generated adequate immune responses.

The safety profile of the Imovax Rabies with up to 5 doses administered as PEP and 3 doses administered as PrEP is well characterized. Imovax Rabies is approved in 15 countries globally (including North America, many European countries, Australia, and New-Zealand) and has been approved for use since 1980 in the U.S. This sBLA proposes to reduce the number of administered doses and as such new safety signals were unanticipated. Therefore, the review of safety data from VAJ00001 and VRV12 focused on identifying new serious adverse events. Due to differences in study design and collection methods, safety data from the two trials were not pooled.

In both studies, solicited local and systemic adverse events (AEs) were collected for seven days after each study vaccine administration and included the expected AEs after IM administration of a vaccine product.

In Study VAJ00001 approximately half of the participants reported at least one solicited reaction. A third of the participants reported at least one solicited local and solicited systemic reaction, each.

No related serious adverse events (SAEs) were reported. One unrelated death was reported: a 2-year-old male participant from the 2-dose Imovax Rabies group died 190 days after his second injection of Imovax Rabies. The cause of death was reported as measles and subsequent community acquired pneumonia, complicated by sepsis.

In Study VRV12 approximately half of the participants experienced at least one solicited injection site and/or systemic reaction. Most reactions were mild to moderate in intensity. No related SAEs, or any deaths were reported.

In summary, the submitted safety data did not identify any new safety concerns indicating that changing the dosing regimen from a 3-dose to 2-dose series poses a safety issue.

Based on the submitted clinical data, the clinical reviewer recommends including the 2-dose PrEP regimen by IM route (1 dose at D0 and 1 dose at D7, 1.0 mL each) in the USPI.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

VAJ00001:

Demographic characteristics of the study population for Groups that received 3-dose versus 2-dose Imovax Rabies PrEP regimens were presented by sex, and age groups (2-11 years, 12-17 years, 18-64 years and ≥65 years).

Subgroup analyses were performed to assess the differences in immune responses between different age groups after a 2-dose and a 3-dose PrEP regimen. Immunogenicity results showed that 14 days after last vaccination with the 2-dose Imovax Rabies PrEP regimen, 100% (100/100) pediatric participants (i.e., 2 through 17 years of age), and 94% (110/117) of adults had an RVNA titer ≥0.5 IU/mL. RVNA titers tended to be higher in children compared with adults. Of note, no adults ≥60 years of age were enrolled into the study.

Approximately equal numbers of male and female participants were enrolled in this study.

The study did not include demographic breakdowns for race and/or ethnicity. The Applicant reported that study VAJ00001 was a non-IND study conducted in the Philippines, where race and ethnicity data collection was not a local regulatory requirement at the time of study design. Available evidence does not indicate substantial differences in safety or effectiveness of rabies vaccine among different racial and ethnic groups. Hence, the lack of such diversity in this study is not considered an issue with regard to broader applicability of the results of immunogenicity assessments.

Study VRV12

Participant demographics were assessed by age (12-23 months, 2-11 years, 12-17 years, 18-40 years, 41-64 years and ≥65 years), sex (female, male), race and ethnicity. Two pediatric participants were in the 12–23-month age group, and two participants were ≥65 years of age.

Subgroup analyses were performed to assess the differences in immune response between subpopulations from different age groups after a 2-dose and a 3-dose PrEP regimen. Immunogenicity results in subpopulations showed that 21 days after last PrEP vaccination of a

2-dose PrEP regimen with Imovax Rabies, all (88/88; 100%) pediatric participants (i.e., between ages 12 months through 17 years) had an RVNA titer ≥0.5 IU/mL. Of note, immunogenicity data are available for only one pediatric participant 12-23 months of age.

From adult participant groups, almost all participants developed RVNA titers of ≥0.2 IU/mL [209/211 (99.1%)] and a majority [204/211 (96.7%)] developed RVNA titer of ≥0.5 IU/mL. Two adult participants, one each in Group 6: 18-40 years of age and 41–64 years of age did not respond (e.g., had RVNA titers <0.2 IU/mL). Only one participant ≥65 years of age had immunogenicity data and that one participant developed RVNA titer of 0.3 IU/mL. In general, RVNA titers tended to be higher in children compared with adults.

Overall, the study included fewer males than females. The racial origin of all participants was Asian, with all participants enrolled in Thailand.

1.2 Patient Experience Data

Patient experience data were not collected to support the proposed change in indication.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Rabies is an acute, progressive viral encephalomyelitis that affects the central nervous system of mammals, including humans. The disease is characterized by severe neurological dysfunction, behavioral changes, and an almost invariably fatal outcome once clinical symptoms manifest. Rabies is caused by viruses belonging to the genus *Lyssavirus* within the family Rhabdoviridae. The classical rabies virus (RABV) serves as the prototype species, but the genus encompasses multiple related viruses capable of causing clinically indistinguishable disease in humans. The RABV genome encodes five proteins including the glycoprotein or G protein, which is the surface-exposed protein on the virus and is the target of vaccine-elicited neutralizing antibodies (Callaway 2022).

Rabies is zoonotic and is most commonly transmitted to humans after exposure to an infected animal's saliva via bite or scratch. Infection may also occur if the virus is introduced through the mucous membranes. Rarely, rabies infections have been reported after exposure to aerosolized rabies virus or after transplantation of an organ from an infected donor.

Following exposure through animal bites or scratches, rabies virus enters peripheral tissues and binds to nicotinic acetylcholine receptors and other cellular receptors at neuromuscular junctions. The virus exploits retrograde axonal transport mechanisms to travel from the peripheral nervous system to the central nervous system (CNS), moving along nerve pathways. Upon reaching the CNS, the virus preferentially targets neurons in the brainstem, which controls vital autonomic functions including respiration, cardiovascular regulation, and swallowing. The virus also affects the limbic system, contributing to the characteristic behavioral changes observed in rabies infection.

The incubation period after exposure ranges from 1 week to more than a year but typically is 1-3 months. Without timely, appropriate PEP following exposure, rabies infection results in progressive encephalitis/myelitis, coma and eventually death.

WHO estimates 59,000 human rabies deaths annually, approximately 95% of which occur in Africa and Asia where canine rabies is endemic; the vast majority (99%) of rabies cases occur

due to exposure to infected dogs (WHO 2025). Successful canine vaccination campaigns have virtually eliminated dog-mediated rabies in the U.S., Western Europe, Japan, Australia and Canada; rare cases have been reported after importation of dogs from other countries where rabies is endemic. Other animals, like bats, foxes and racoons are responsible for rabies exposure in countries where canine rabies has been eliminated (Plotkin 2000).

The major current reservoirs of rabies in the U.S. are primarily wildlife, particularly bats, raccoons, skunks, and foxes. Despite the presence of these infected animal populations, human rabies cases remain rare in the U.S. Twenty-five rabies cases have been reported in the U.S. from 2009-2018, including seven cases that were acquired outside the U.S. and its territories (CDC 2024). Approximately 30,000-60,000 persons in the U.S. receive rabies PEP per year; approximately 30-40% receiving PEP are children. Data are lacking for the number of people in the U.S. receiving PrEP per year, but one estimate based on mathematical modeling indicates that approximately 60,000 people receive PrEP, with approximately 2/3 of them being travelers (Rao 2021).

Untreated rabies infection is virtually 100% fatal. Pre-exposure vaccination against rabies and timely post-exposure vaccination [with or without administration of rabies immunoglobulin (RIG), depending on rabies vaccination status] are the cornerstones for prevention of rabies disease.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

KEDRAB is a human rabies immune globulin (HRIG) indicated for passive, transient PEP of rabies infection given immediately after contact with a rabid or possibly rabid animal (if indicated, depending on Rabies vaccination status). KEDRAB should be administered concurrently with a full course of rabies vaccine.

2.3 Safety and Efficacy of Pharmacologically Related Products

In addition to Imovax Rabies, one other cell culture (purified chick embryo cell) vaccine, RabAvert, is licensed in the U.S. for PrEP and PEP against rabies. Both vaccines are similarly well tolerated with no identified safety issues. Both vaccines are approved in the U.S. as 3-dose PrEP regimen and 5-dose PEP regimen.

Globally, multiple other vaccines are available, such as human diploid cell vaccine (HDCV) produced by Chengdu Kanghua Biological Products China (Kanghua Rabies); Purified chick embryo cell vaccine (PCECV) produced by Cadila Healthcare India (Vaxirab-N); Purified Vero cell rabies vaccine (PVRV) produced by Serum Institute India (RABIVAX-S), Chengda Bio China (SPEEDA), Human Biologicals Institute India (Abhayrab), and Bharat Biotech India (Indirab); Purified duck embryo vaccine (PDEV) produced by Cadila Healthcare in India (Lyssavac, Vaxirab); primary Syrian hamster kidney cell vaccine (PHKCV) from local producers in China; and Baby hamster kidney cell vaccine (BHKV) produced in Russia (Kokav).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Imovax Rabies is indicated for PrEP and PEP against rabies and is approved for use in the U.S. for all age groups. It was first licensed (in Cameroon) in 1975 and received U.S. approval for use in 1980. It is currently licensed for use in 15 countries, including 8 countries in the European Union.

In accordance with the current (October 2019) PI, Imovax Rabies is indicated for IM administration as:

- PrEP as "three 1.0 mL doses of Imovax Rabies vaccine administered IM…one injection per day on Days 0, 7, and 21 or 28." Instructions for timing and frequency of the booster dose (one injection of 1.0 mL of Imovax Rabies) following a pre-exposure regimen (and without known exposure) is based on the level of risk of exposure to the virus (continuous, frequent, infrequent, and rare).
- PEP for previously unvaccinated persons as "5 intramuscular doses (1 mL each) of Imovax Rabies vaccine, one dose immediately after exposure (Day 1) and one dose 3, 7, 14 and 28 days later." RIG is administered on Day 0 in conjunction with the first vaccine dose in accordance with the PI.
- PEP for previously immunized persons who are potentially exposed to the rabies virus "should receive two intramuscular doses (1.0 mL each) … one dose immediately after the exposure and one dose 3 days later. RIG should not be given in these cases."

Recommendations for PrEP and PEP rabies vaccinations are periodically reviewed nationally and internationally to optimize public health outcomes. In 2018, after such a review, WHO revised their recommendations for IM administration of PrEP from a 3-dose regimen administered over 3 to 4 weeks to a 2-dose PrEP regimen administered over 1 week.

In 2021, the ACIP Rabies Work Group re-evaluated their recommendations for PrEP. The following concerns regarding the PrEP recommendations were identified by the committee; the cost of a 3-dose PrEP series, non-compliance with recommendations for titer checks in persons at higher risk of rabies exposure and confusion about the risk categories which determine the timing of rabies vaccine booster doses. As the largest group of individuals receiving PrEP is travelers to countries where canine rabies is endemic, an additional concern was the relatively long period (minimum of 21 days) to completion of the 3-dose PrEP series.

After a systematic review of 12 studies evaluating IM and intradermal administration of PrEP in 1401 participants, the ACIP concluded that the immunogenicity of the 1-week (Days 0 and 7) 2-dose PrEP schedule was comparable to the 3-dose PrEP schedule (Rao 2022).

The Applicant's rationale for conducting Study VAJ00001, which was initiated in 2018 following the updated WHO recommendations, was to compare shorter vaccination schedules with previously recommended, longer schedules, noting that it is critical to demonstrate that a shorter schedule "offers an adequate immune priming thus allowing for a rapid reappearance of rabies virus neutralizing antibodies after a post-exposure dose."

Based on the results of Study VAJ00001, the 2-dose PrEP regimen was approved in France in July 2022, as well as Denmark, Finland, Germany, Ireland, Netherlands, Norway, Spain, Sweden and in the United Kingdom.

The Applicant states that no postmarketing data are available for 2-dose PrEP regimen since this schedule has been recently approved. Moreover, the Applicant states that it is difficult to retrieve postmarketing data coming only from individuals who have received the 2-dose regimen, as this regimen overlaps with the 3-dose regimen.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

- November 15, 2021- Type B meeting request (subsequently converted to a Type C meeting) to discuss update to Imovax Rabies PI to include an alternate PrEP immunization schedule.
- March 30, 2022 - FDA provided a Written Response Only (WRO) for Type C meeting
- April 20, 2022 - sBLA submission for 2-dose Imovax PrEP supported by non-IND study VAJ00001 (103931/5296)
- December 09, 2022 - FDA advice under 103931/5296 recommending withdrawal of sBLA and suggested revisions to VRV12 that would not require licensure of 2-dose Imovax to license 2-dose VRVg
- December 20, 2022 - Applicant requested withdrawal of sBLA 103931/5296
- January 5, 2023 - 103931/5296 withdrawn (letter sent)
- March 03, 2023 - Applicant submitted 15026.106 (responding to FDA December 09, 2022 communication) in which the Applicant suggested to add 2 new secondary objectives to ongoing study VRV12 to support a 2-dose PrEP for Imovax Rabies.
- April 07, 2023 FDA sent IR (under 15026) requesting clarification of amendment 106
- April 12, 2023 – Applicant submitted 15026.108 to respond to the FDA's IR from April 07, 2023. The response had no new information, but a clearer presentation of objectives, hypotheses, statistical success criteria, and whether an objective is dependent on success of another.
- May 22, 2023 – FDA feedback to Applicant regarding 15026.106 in which FDA affirmed position that the -5% margin, used throughout the VRVg program, is the appropriate margin for demonstrating noninferiority of the proposed 2-dose vs. conventional 3-dose rabies pre-exposure regimens.
- August 18, 2023 – Applicant submitted revised VRV12 protocol with added objectives, including a comparison of 2- and 3-dose Imovax Rabies with a -10% margin [IND 15026.119 (seq 0110)]
- November 02, 2023 - FDA advised applicant noting that -10% margin for this product is contrary to FDA's -5% advice, and that the Applicant proceeded at risk if they continued with the -10% margin (under IND 15026)
- February 21, 2024 – FDA advised Applicant to request a meeting to discuss sBLA for 2-dose Imovax Rabies after they informed FDA via email of their intent to submit a 2-dose PrEP sBLA (communication to Applicant under IND 15026)
- March 18, 2024 – Applicant submitted Type C meeting request to discuss submission of an sBLA for 2-dose Imovax Rabies PrEP supported by VAJ00001 and interim results from VRV12 (103931/5333)
- May 31, 2024 - FDA responses (WRO) were sent to the applicant, advising Applicant on what to include in a 2-dose Imovax Rabies PrEP sBLA
- September 23, 2024 – The Applicant submitted sBLA 103931/5342

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated for a complete clinical review without unreasonable difficulty. The Applicant submitted standardized Study Data Tabulation Model (SDTM) datasets and Analysis Data Model (ADaM) datasets for both Studies VAJ00001 and VRV12. The datasets were validated, and several relatively minor data quality and compliance issues were identified related to data collection and reporting and dataset inconsistencies.

Ultimately the identified issues did not impact the ability to review and draw conclusions from the data.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Both studies VAJ00001 and VRV12 were conducted outside of the U.S. Study VAJ00001 was a non-IND study while VRV12 was conducted under IND. Both VAJ00001 and VRV12 were conducted in compliance with Good Clinical Practice (GCP) as defined by ICH E6 Guideline for GCP and met the requirements of the Declaration of Helsinki as set forth by the World Medical Association.

Bioresearch Monitoring (BiMO), Division of Inspections and Surveillance, Office of Compliance and Biologics Quality, conducted an inspection of two clinical study sites for study VRV12 in Thailand:

- Site 764-0001: Dr. Terapong Tantawichien (Bangkok, Thailand) and
- Site 764-0003: Dr. Kulkanya Chokephaibulkit (Bangkok, Thailand).

The inspected sites represented approximately 64% of the total enrollment of the total study population.

In addition, the Applicant provided copies of two previously conducted BiMO inspection reports of the two study sites of VAJ00001 in the Philippines:

- Study site # 001, Dr. Beatriz Quiambao and
- Study site # 002, Dr. Jonathan Lim.

Reviewer comment: The inspections did not reveal deficiencies that would preclude approval. Please see the BiMO review memos for details.

3.3 Financial Disclosures

The Applicant made reasonable efforts to obtain financial disclosure from all investigators and sub-investigators who participated in the covered studies as defined in 21 CFR 54.2(e) submitted to the sBLA.

In the Financial Certification and Disclosure Form, the Applicant listed all the investigators in the covered studies, and certified that no financial arrangements with an investigator had been made where study outcome could affect compensation; that the investigator had no proprietary interest in the tested product; that the investigator did not have a significant equity interest in the sponsor of the covered study; and that the investigator had not received significant payments or other types.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

No substantial issues were identified by the discipline reviewer. Please refer to Chemistry, Manufacturing and Controls (CMC) review memo for a detailed CMC assessment.

4.2 Assay Validation

The RFFIT assay was used for immunogenicity assessments. Assessments were conducted at the Applicant's Global Clinical Immunology laboratory in the U.S.

The RFFIT assay was appropriate for the clinical application and was validated for its intended use. The lower limit of quantification (LLOQ) of the assay was defined as 0.2 IU/mL.

Reviewer Comment: Virus neutralization assays such as the RFFIT are among the most widely used and accepted methods of detecting the presence of antibodies against the rabies virus and are considered reliable indicators of active immunization following vaccination (WHO 2017). The RFFIT is considered the gold standard assay for measurement of RVNAs.

- *Titer threshold for adequate immune response: An RVNA titer of ≥0.5 IU/mL was established during the 1978 Joint WHO/International Association of Biological Standardization (IABS) symposium as a minimum level to demonstrate seroconversion 4 weeks after a vaccination series (WHO 2017). It is widely accepted as an indicator for vaccine-mediated protection against rabies (WHO 2018). A level of 0.5 IU/mL is considered conservative and helps to mitigate the effects of variability inherent in the virus neutralizing assays. Support for this threshold as being appropriately conservative include the following:*
  - *Protection against rabies was demonstrated in cats and dogs at RVNA levels of 0.1 IU/mL and 0.2 IU/mL, respectively (WHO 2017).*
  - *Prior to 2021/2022, the ACIP specified complete neutralization of rabies virus at a 1:5 dilution by RFFIT (roughly correlating to a titer of 0.1-0.3 IU/mL) as evidence of vaccine-mediated rabies virus protection; no rabies infections occurred when individuals were deemed protected at that threshold (Rao 2022).*
- *Timing of evaluation of the titer: In PrEP clinical trials, blood drawn between Day 14 and 35 after initiation of vaccination and assayed to confirm the presence of RVNA can provide the evidence needed to confirm that the regimen under consideration is immunogenic (Briggs et al. 2022). While acceptable to evaluate the RVNA titer at Day 14, a longer time interval from the first vaccination to the RVNA titer check may allow for more maturation of immune responses and subsequently better account for differences in kinetics of immune responses, as the vaccine response may reach its highest level later, at Day 30 (Xu et al. 2021).*

4.3 Nonclinical Pharmacology/Toxicology

Nonclinical developmental toxicity studies have not been conducted with Imovax Rabies vaccine.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Protection after vaccination is provided by the induction of measured rabies virus neutralizing antibodies (RVNA).

4.5 Statistical

No major statistical issues were identified at the time when the clinical review was finalized. See statistical review memo for details.

4.6 Pharmacovigilance

Routine pharmacovigilance activities are planned by Sanofi. Please refer to Office of Biostatistics and Pharmacovigilance (OBPV) review memo for details.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The clinical reviewer focused on the review of effectiveness data from clinical study VRV12 with a targeted review of effectiveness data from Study VAJ00001 as supportive data. Since Imovax Rabies has been approved for use in the U.S. since 1980, and the focus of the current BLA supplement is to reduce the PrEP vaccination series from 3 doses of Imovax Rabies to 2 doses administered via the same intramuscular route, the review of the safety data focused mainly on evaluating any unusual adverse events not previously described in the product package insert. The Applicant did not submit an Integrated Summary of Efficacy (ISE) or an Integrated Summary of Safety (ISS) since differences in the two study designs precluded integration of the data.

Both studies VAJ00001 and VRV12 included evaluation of products or administration routes that are not relevant to this sBLA submission, hence these data were not reviewed.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following modules and supporting document were comprehensively reviewed:

- STN 103931/5342 Module 1.2 (Reviewer's guide, Reviewers Guide Annex 1 through 4).
- STN 103931/5342 Module 1.3.4 (Financial Disclosure)
- STN 103931/5342 Module 1.6.3 (Meetings)
- STN 103931/5342 Module 1.9.4 (Proposed Pediatric Study Request and Amendments)
- STN 103931/5342 Module 1.14 (Labeling)
- STN 103931/5342 Modules 2.5, 2.7.3, 2.7.4 and 2.7.6 (Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and Synopses of Individual Studies)
- STN 103931/5342 Module 5.2 (Tabular Listing of all Clinical Studies)
- STN 103931/5342 Module 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claims Indication)
- STN 103931/5342/5003 Module 1.11.3 (Response to CBER's IR#3 regarding applicability of Foreign Data)
- STN 103931/5342/5004 Module 1.11.3 (Response to CBER's IR #4 regarding request for additional information about the participants with possible rabies exposure and subsequent outcomes)
- STN 103931/5342/5005 Module 1.11.3 (Response to CBER's IR #5 regarding request for program code used to generate the tables submitted in response to IR #4)
- STN 103931/5342/5006 Module 1.11.3 (Response to CBER's IR #6 regarding request for table programs and primary support macros for datasets)
- STN 103931/5342/5008 Module 1.11.3 (Response to CBER's IR #8 regarding request to clarify whether race and ethnicity data was collected in study VAJ00001)
- STN 103931/5342.5009 Module 1.14.1 (Response to CBER's IR #9 regarding comments related to the proposed Prescribing Information and proposed revised Prescribing Information)
- STN 103931/5342.5009 Module 1.11.3 (Response to CBER's IR#10 related to Table 2 from the Prescribing Information)

- STN 103931/5342.5010 Module 1.11.3 (Response to CBER's IR #11 regarding dataset validation issues)
- STN 103931/5342.5011 Module 1.14.1 (Response to CBER's IR #12 regarding comments related to the proposed Prescribing Information and proposed revised Prescribing Information)
- STN 103931/5342.5012 Module 1.11.3 (Response to CBER's IR #13 dataset comments)
- STN 103931/5342.5013 Module 1.11.3 (Response to CBER's IR #14 regarding follow-up dataset comments communicated in the Applicant response to IR#11)
- STN 103931/5342.5014 Module 1.11.3 (Response to CBER's IR #15 regarding subjects who did not respond to vaccination)
- STN 103931/5342.5016 Module 1.14.1 (Response to CBER's IR #16 regarding Prescribing Information)
- STN 103931/5342.5017 Module 1.14.1 Response to CBER's IR #17 regarding Prescribing Information)
- STN 103931/5342.5018 Module 1.14.1 (Response to CBER's IR #18 regarding Prescribing Information)
- STN 103931/5342.5019 Module 1.14.1 (Response to CBER's IR #19 regarding Prescribing Information)

5.3 Table of Studies/Clinical Trials

The clinical trials that are considered essential to support the proposed indication and usage are reviewed in detail in section 6 and summarized in Table 1. Note that both studies included evaluation of products or administration routes that are not relevant to this sBLA submission and will not be discussed further.

Table 1. Summary of Clinical Studies for sBLA 103931/5342 Essential to Support the Application

Study Number	Study Design	Dosing Regimen	Study Participants (n)	Primary Endpoints
VAJ00001 NCT# 03700242 Non-IND study	Phase 3, open-label, randomized, multicenter, active-controlled	Dosage **1 IM dose (Imovax Rabies) = 1.0 mL** 1 IM dose (Verorab) = 0.5 mL 1 ID dose (Imovax Rabies or Verorab) = 0.1 mL PrEP regimens evaluated: **Group 1: 1 IM dose of Imovax Rabies on Day 0 and D7 (2-dose PrEP)** **Group 2: 1 IM dose of Imovax Rabies on D0, D7, and D21 (3-dose PrEP)** Group 3: 2 ID doses of Imovax Rabies on D0 and D7 (2-dose PrEP) Group 4: 1 IM dose of Verorab on D0 and D7 (2-dose PrEP) Group 5: 2 ID doses of Verorab on D0 and D7 (2-dose PrEP) **Simulated PEP Regimens:** **Group 1: 1 IM dose of Imovax Rabies on Year 1 and Y1 + 3 days** **Group 2: 1 IM dose of Imovax Rabies on Y1 and Y1 + 3 days**	570 total: **Group 1: 228,** **Group 2: 115**, Group 3: 77, Group 4: 75, Group 5: 75	NI of IM 2-dose PrEP vs IM 3-dose PrEP with Imovax Rabies assessed as % with RRFIT >=0.5 IU/mL

Study Number	Study Design	Dosing Regimen	Study Participants (n)	Primary Endpoints
		Group 3: 1 ID dose of Imovax Rabies on Y1 and Y1+3 Days Group 4: 1 IM dose of Verorab on Y1 and Y1+3 Days Group 5: 1 ID dose of Verorab on Y1 and Y1+3 days		
VRV12 NCT# 04127786 IND study	Phase 3, observer-blind, randomized, multicenter, active-controlled	**Dosage** 1 IM dose VRVg-2 = 0.5mL 1 IM dose Verorab = 0.5mL **1 IM dose Imovax Rabies = 1.0mL** **PrEP regimens** Cohort 1 (pediatric and adult participants) Group 1: 1 IM dose of VRVg-2 on D0, D7 and D28 Group 2: 1 IM dose of Verorab on D0, D7 and D28 **Group 3: 1 IM dose of Imovax Rabies on D0, D7 and D28** Adult subsets from each group received 1 IM dose of VRVg-2 at M12 (booster) Cohort 2: Adults only Group 4: 1 IM dose of VRVg-2 on D0 and D7 Group 5: 1 IM dose of Verorab on D0 and D7 Group 6: 1 IM dose of Imovax Rabies on D0 and D7 All groups included adult subset who received 1 IM dose of VRVg-2 at M24-36 (booster)	1708 total: Group 1: 607, Group 2: 202, **Group 3: 200**, Group 4: 419 Group 5: 139, **Group 6: 139**	NI of the 2nd formulation of purified vero rabies vaccine global – serum free (VRVg-2) vs Verorab and Imovax Rabies following a 3-dose PrEP regimen (Cohort 1)*

Source: FDA-generated table
Abbreviations: sBLA=supplemental Biologics License Application; IM=Intramuscular; ID=Intradermal; NI=Noninferior; PrEP=Pre-exposure prophylaxis; PEP=Post exposure prophylaxis; Imovax Rabies=Sanofi Pasteur human diploid cell vaccine; Verorab=Sanofi Pasteur purified vero cell rabies vaccine.
Notes: * VRV12 primary immunogenicity endpoint is not relevant to this sBLA. The 5th and 6th immunogenicity objectives and endpoints are discussed in sections 6.2.1 Objectives and 6.2.8 Endpoints and Criteria for Study Success.

5.4 Consultations

The file was presented to the Pediatric Review Committee (PeRC). PeRC discussed the age group should FDA approve this product. As Imovax Rabies is already approved without age restriction, PeRC stated that an age limit should not be imposed on this application/product (please refer to Section 9.1.3 for further details).

5.4.1 Advisory Committee Meeting

Not applicable.

5.4.2 External Consults/Collaborations

Not applicable.

5.5 Literature Reviewed

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Rao, A K. (2021) Summary of Evidence to Recommendations Framework for Rabies Pre-Exposure Prophylaxis Vote. Presentation. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwjt2M7ik6aNAxUzSPEDHe9UAjkQFnoECBgQAQ&url=https%3A%2F%2Fstacks.cdc.gov%2Fview%2Fcdc%2F109103%2Fcdc_109103_DS1.pdf&usg=AOvVaw2gpK9F_I1hkk4vqBIAcv4T&opi=89978449

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Study VAJ00001 was a Phase 3 multi-center, prospective, active controlled study with a planned enrollment of 570 participants ≥2 years of age randomized into 5 groups to receive either Imovax Rabies or Verorab intradermally (ID) or IM on a PrEP regimen, followed by administration of booster doses on a simulated PEP (sPEP) regimen.

Reviewer Comment: The study protocol was not submitted to CBER for review and comment prior to initiation. Verorab is not licensed for use for rabies PEP or PrEP in the U.S., and Imovax Rabies is not approved for ID administration in the U.S., hence only data applicable to the U.S. population (Imovax Rabies administered IM) will be discussed in this memo, except when discussing general study design.

Simulated post-exposure prophylaxis in the context of rabies refers to a clinical scenario or study where rabies PEP is administered, but without an actual rabies exposure event having occurred. It involves giving the vaccine and, in some cases, human rabies immune globulin (HRIG) to individuals who have not been exposed to a rabid animal, mimicking the treatment given after an exposure.

The study was initiated on September 26, 2018, and completed on April 08, 2020.

6.1.1 Objectives

Primary study objective:

- To demonstrate that a short (1-week, 2-dose) Imovax Rabies IM PrEP regimen is NI to the reference (3-week, 3-dose) Imovax Rabies IM PrEP regimen in terms of seroconversion rate (SCR) 14 days after the last PrEP vaccination with Imovax Rabies (Group 1 versus Group 2).

Secondary study objectives

Immunogenicity of the PrEP regimen

- To describe in each group the RVNA titers at baseline and at 14 days after the last Imovax Rabies vaccination when administered as a PrEP regimen.

Antibody persistence

- To describe in each group the RVNA titers 6 months and 1 year after the last PrEP vaccination with Imovax Rabies.

Immunogenicity of the sPEP regimen

- To describe in each group the immune response induced by Imovax Rabies when administered as an sPEP regimen, 7 and 14 days after the sPEP regimen.

Safety

- To describe in each group the safety profile of Imovax Rabies after each and any injection when administered as a PrEP regimen.
- To describe in each group the safety profile of Imovax Rabies after each and any injection when administered as an sPEP regimen 1 year after the last PrEP vaccination.

6.1.2 Design Overview

A total of 570 participants ≥2 years of age were planned for 6:3:2:2:2 randomization into the following 5 groups at study entry to receive a primary vaccination regimen (PrEP phase of study) of Imovax Rabies or Verorab in an open-label manner:

- Group 1 – 1 IM dose of Imovax Rabies (1.0 mL) on D0 and D7 (N=228)
- Group 2 – 1 IM dose of Imovax Rabies (1.0 mL) on D0, D7 and D21 (reference group, N=114)
- Group 3 – 2 ID doses of Imovax Rabies (2 x 0.1 mL) on D0 and D7 (N=76)
- Group 4 – 1 IM dose of Verorab (0.5 mL) on D0 and D7 (N=76)
- Group 5 – 2 ID doses of Verorab (2 x 0.1 mL) on D0 and D7 (N=76)

One year after the last PrEP injection (Y1), all participants were scheduled to receive an sPEP regimen (PEP phase) for pre-immunized individuals consisting of 2 post-exposure doses of Imovax Rabies or Verorab as follows:

- Group 1 – 1 IM dose of Imovax Rabies on Y1 and Y1 + 3 days
- Group 2 – 1 IM dose of Imovax Rabies on Y1 and Y1 + 3 days
- Group 3 – 1 ID dose of Imovax Rabies on Y1 and Y1 + 3 days
- Group 4 – 1 IM dose of Verorab on Y1 and Y1 + 3 days
- Group 5 – 1 ID dose of Verorab on Y1 and Y1 + 3 days

Reviewer Comment: Safety and immunogenicity data in Groups 3-5 are not considered relevant for the USPI because they were generated using vaccine that is either not licensed in the U.S. or given by a route of administration not approved in the U.S. Therefore, these data were not reviewed and are not included in this memo. The disposition of participants in these groups was reviewed from the perspective of evaluating the overall quality of study conduct and is not discussed further, as this information did not raise concerns.

Administration of 2-dose sPEP instead of a single booster dose has more relevance for rabies-endemic countries as compared with non-rabies endemic countries like the U.S. Had CBER had the opportunity to provide comments on the study protocol, (b) (5) .

Additionally, administration of sPEP to pediatric study participants, unlike primary series rabies vaccination, constitutes greater than minimal risk without prospect of direct benefit (45 CFR Part 46 Subpart D). As such, had CBER had the opportunity to provide comments on the study protocol in which sPEP was delineated as an intervention, (b) (5)

The study included five PrEP phase visits on Days 0, 7, 21, 35 and 180 (Visits 01, 02, 03, 04 and 06) for 2-dose group. Three-dose group had an additional PrEP phase visit on Day 49 (Visit 05). All participants had five sPEP phase visits at Y1, Y1 + 3 days, Y1 + 7days, Y1 + 14 days and Y1 + 31 days (Visits 07, 08, 09, 10 and 11, respectively). Planned participant study participation time was 403 - 436 days.

All participants were scheduled for six 5 mL blood draws during the study for immunogenicity assessment; at baseline prior to first vaccination (V01/D0), 14 days after last PrEP phase vaccination (V02/D21 for 2-dose group and V03/D35 for 3-dose group), at M6 and Y1, Y1 + 7 days and Y1 + 14 days after last PrEP vaccination.

6.1.3 Population

Inclusion criteria (all criteria must have been met to qualify for study enrollment)

- Age ≥2 on the day of inclusion
- For participants <18 years of age: Assent form signed and dated by the participant (as appropriate) and informed consent form (ICF) signed and dated by parent/legally authorized representative (LAR). For participants ≥18 years of age, ICF signed and dated.
- Participant (and parent/LAR if applicable) is able to attend all visits and comply with trial procedures.

Select exclusion criteria

- Participant is pregnant, lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to first vaccination until 4 weeks after last vaccination. Non-childbearing potential was defined as pre-menarche, post-menopausal for at least one year, or surgically sterile.
- Previous vaccination at any time against rabies with the trial vaccines or other vaccines
- Receipt of blood, blood-derived products and immune globulins within the preceding 3 months
- Known or suspected congenital or acquired immunodeficiency, receipt of immunosuppressive therapy within the preceding 6 months, or long-term systemic corticosteroid therapy within the past 3 months
- Alcohol abuse or drug addiction
- Participation at the time of study enrollment or planned participation in the 4 weeks prior to first trial vaccination in a clinical trial investigation of a vaccine, drug, medical device or procedure
- Receipt of any vaccine in the 4 weeks preceding first trial vaccination or planned receipt of any vaccine in the 4 weeks following any trial vaccination except for influenza vaccination which may be received at least 2 weeks before study vaccines
- Receipt of chloroquine or other medications used for malaria chemoprophylaxis, with or without other anti-malarial treatment, for more than 4 weeks (duration of anti-malarial course) and part of the treatment received within the 2 weeks before vaccination, contraindicating intradermal vaccination

Reviewer Comments: The eligibility criteria were reasonable for the study.

According to CDC (CDC, 2025), concomitant use of chloroquine can reduce the antibody response to rabies vaccine administered ID as a preexposure vaccination. ID administration of rabies vaccine is not currently approved for use in the U.S.

Children <2 years of age were not eligible for enrollment. The Applicant cited difficulty in enrolling participants <2 years of age; and their Pediatric Study Plan provided a rationale for extrapolation from older to the <2 years of age pediatric age group.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Imovax Rabies and Verorab were administered both IM and ID. Only the Imovax Rabies administered IM will be described here.

The Imovax Rabies drug substance consists of inactivated rabies virus (Wistar Rabies Pittman Moore/WI 38 1503-3M strain), produced in human diploid/MRC-5 cells. It is concentrated by ultrafiltration and the virus is inactivated with beta-propiolactone.

Each 1 mL dose of reconstituted vaccine also contains the following components: Inactivated rabies virus: ≥2.5 IU; Human albumin: ≤100 mg; Neomycin: <150 µg; Phenol red: 20 µg; Sterile water for injection: 1 mL. Volume of the IM dose was 1.0 mL.

6.1.5 Directions for Use

Participants in 2-dose group received 1 IM dose of Imovax Rabies (1.0 mL) on D0 and D7, and 1 IM dose at Y1 and Y1+3 days.

Participants in 3-dose group received 1 IM dose of Imovax Rabies (1.0 mL) on D0, D7 and D21, and 1 IM dose at Y1 and Y1+3 days.

6.1.6 Sites and Centers

The study was conducted at two centers in the Philippines, with two Principal Investigators: Beatriz Quiambao MD and Jonathan Lim MD.

6.1.7 Surveillance/Monitoring

Safety assessment-solicited AEs

Participants were issued diary cards to record solicited symptoms daily from the day of injection and within 7 days after each vaccination.

In addition, during the sPEP vaccination phase, solicited systemic reactions between the first and second injection, and up to the 7 days after the second injection were collected.

Diary card

The diary card solicited the following injection site and systemic reactions:

- Injection site pain, injection site erythema, injection site swelling
- Fever, headache, malaise, myalgia

Participants or their parent/LAR were provided with a digital thermometer and ruler to aid in documentation and measurement of solicited reactions. For measurable reactions (injection site erythema and swelling), the participants or their parent/LAR were to record the actual measurement, with the classification of grade assigned at the time of the statistical analysis. Additionally, the study participant or their parent/LAR were to document the route by which temperature was taken and whether any action was taken for each reaction (e.g., medication, health care provider contacts with or without medication, hospitalization).

Intensity grading scales for solicited systemic reactions were consistent across age groups; these reactions were graded as follows:

- Fever:
    - Grade 1: ≥38°C to ≤38.4°C

  - Grade 2: ≥38.5°C to ≤38.9°C
  - Grade 3: ≥39°C
- Non-ordinal solicited systemic reactions:
  - Grade 1: no interference with activity
  - Grade 2: some interference with activity
  - Grade 3: significant, prevents daily activity

The intensity grading scale for solicited injection site reactions for children 2-11 years of age was as follows:

- Injection site pain
  - Grade 1: Easily tolerated
  - Grade 2: Sufficiently discomforting to interfere with normal behavior or activities
  - Grade 3: Incapacitating, unable to perform usual activities
- Injection site erythema
  - Grade 1: >0 to <25 mm
  - Grade 2: ≥25 mm to <50 mm
  - Grade 3: ≥50 mm
- Injection site swelling
  - Grade 1: >0 to <25 mm
  - Grade 2: ≥25 mm to <50 mm
  - Grade 3: ≥50 mm

The intensity grading scale for solicited injection site reactions for participants ≥12 years of age was as follows:

- Injection site pain
  - Grade 1: No interference with activity
  - Grade 2: Some interference with activity
  - Grade 3: Significant, prevents daily activity
- Injection site erythema
  - Grade 1: ≥25 mm to ≤50 mm
  - Grade 2: ≥51 mm to ≤100 mm
  - Grade 3: >100 mm
- Injection site swelling
  - Grade 1: ≥25 mm to ≤50 mm
  - Grade 2: ≥51 mm to ≤100 mm
  - Grade 3: >100 mm

Reviewer Comment: Study procedures for collecting solicited AEs and the grading scales used were acceptable for this study.

Safety assessment-unsolicited AEs

Unsolicited non-serious AEs were collected and recorded for 28 days following each vaccination in the PrEP phase. In the sPEP vaccination phase, solicited systemic reactions between the first and second injections and up to 28 days after the second injections were recorded.

Participants and their parent/LAR were instructed to record medical events that occurred between each PrEP vaccination and for 28 days after the last PrEP vaccination on the diary card. For each unsolicited non-serious AE, the following was recorded:

- Start and stop date of the AE
- Intensity of the AE
    - Grade 1: no interference with activity
    - Grade 2: some interference with activity
    - Grade 3: significant, prevents daily activity
- Action taken for each AE
- Whether the AE led to discontinuation
- Whether the (unsolicited systemic) AE was related to vaccination

The investigator determined the causal relationship between each unsolicited systemic AE and vaccination as either related or not related.

Following the investigator's assessment of causality, the Applicant's Global Safety Officer also assessed the causal relationship based on available information and current medical knowledge.

Reviewer Comment: The diary cards used for collection of solicited AEs and unsolicited AEs during the 30-day postvaccination period were appropriately designed for the intended use.

The study was open label.

Safety assessment-SAEs

The standard time period for reporting SAEs was:

- All SAEs:
    - In the PrEP vaccination phase from first vaccination to V4 (D35) for 2-dose group or V5 (D49) for 3-dose group.
    - In the sPEP vaccination phase between V7 (Y1, 1st sPEP dose) and V11 (Y1+31 days, i.e., 28 days after 2nd sPEP dose).
- All related SAEs, unrelated deaths and life-threatening SAEs that occurred between the end of the PrEP vaccination phase (Visit 4 for 2-dose group or Visit 5 for 3-dose group) and Y1 were collected.

Reviewer Comment: Although the sPEP safety follow-up period was brief and did not collect MAAEs, Imovax Rabies has a well characterized safety profile and has been widely used globally as PEP for several decades without an identified safety signal.

Safety assessment-laboratory AEs and pregnancies

The Applicant collected and reported all pregnancies that occurred throughout the trial. Pregnancy itself was not considered an AE, but any complications during pregnancy were considered as AEs, and in some cases could be considered SAEs. Spontaneous abortions, fetal death, stillbirth, and congenital anomalies reported in the baby were always considered as SAEs.

Clinical laboratory evaluations were not performed in this study.

Adverse events of special interest (AESIs) were not collected in this study.

Assessment-concomitant medications and vaccinations

Documentation of concomitant medications in the eCRF was limited to specific categories of medications that were of interest, beginning on the day of vaccination to the end of the solicited and unsolicited follow-up period (e.g., 28-day safety follow-up). Information reported in the eCRF for these medications were limited to the Filipino trade name, medication category, start and stop dates and whether it was given as treatment or prophylaxis. Reportable medications were in two categories:

- Category 1: antipyretics, analgesics, non-steroidal anti-inflammatory drugs, corticosteroids and other immune modulators
- Category 2 (drugs and therapies pertaining to definitive contraindications): vaccines (except influenza vaccines), chloroquine and other antimalarials, blood or blood derived products, immunosuppressive therapies (duration and types specified), rabies vaccines or RIG.

Reviewer comment: The selective reporting of concomitant medications in this submission presents a limitation for comprehensive safety evaluation, as complete concomitant medication documentation is typically essential for establishing product safety profiles. However, given the well-characterized nature of this vaccine, the primary concern centers on whether anti-inflammatory agents and immunosuppressive therapies may have compromised immune responses to the vaccination regimen, including timing-dependent effects and impact on vaccine immunogenicity. While selective reporting may obscure potential interactions, a targeted approach focusing specifically on immunosuppressive agents and anti-inflammatory medications is probably acceptable in this submission with the goal of determining whether anti-inflammatories and immunosuppressants adversely affected the immune responses of this 2-dose regimen.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint

Participants with a RVNA titer of ≥0.5 IU/mL as measured by the RFFIT 14 days after the last PrEP regimen vaccination [D21 for Group 1 (2-dose), Day 35 for Group 2 (3-dose)].

> *Reviewer Comment: The primary endpoint participants with a RVNA titer of ≥0.5 IU/mL as measured by the RFFIT is appropriate. However, the timing of the assessment is a shorter interval than normally used in vaccine studies (i.e. 14 days post last vaccine dose vs 21 or 28 days post last vaccine dose).*

Secondary endpoints

Immunogenicity of the PrEP regimen

- Participant RVNA titer at D0 and 14 days after the last PrEP vaccination
- Seroconversion of participants at D0 and 14 days after the last PrEP vaccination
- Seropositivity of participant (RVNA titer ≥LLOQ of the RFFIT) at D0 and 14 days after the last PrEP vaccination
- Participant RVNA titer ratios 14 days after the last PrEP vaccination/D0

Antibody persistence

- Participant RVNA titer 6 months and 1 year after the last PrEP vaccination
- Seroconversion and seropositivity of participant 6 months and 1 year after the last PrEP vaccination
- Participant RVNA titer ratios

- 6 months/14 days after the last PrEP vaccination
- 1 year/14 days after the last PrEP vaccination

Immunogenicity of the sPEP regimen

- Participant RVNA titer 7 and 14 days after the first sPEP vaccination
- Seroconversion of participants 7 and 14 days after the first sPEP vaccination
- Participant RVNA titers 7 and 14 days after the first sPEP vaccination/1 year after the last PrEP vaccination

Safety endpoints

- Occurrence of any unsolicited systemic AEs reported in the 30 minutes after each vaccination
- Occurrence of solicited injection site reactions occurring within 7 days after each vaccination
- Occurrence of systemic solicited reactions; during the PrEP phase, within 7 days after each vaccination and during the sPEP phase, between the first and second vaccination and within 7 days after the second vaccination
- Occurrence of unsolicited, non-serious (spontaneously reported) injection site reactions within 28 days after each vaccination
- Occurrence of non-serious unsolicited systemic AEs between each vaccination and within 28 days after the last vaccination (PrEP and sPEP)
- Occurrence of SAEs throughout each phase as follows:
  - PrEP phase: from Day 1 to Day 35 (Group 1) or Day 49 (Group 2)
  - PEP phase: from Y1 to Y1+31 days.
- Related SAEs, unrelated deaths and life-threatening SAEs will be collected between PrEP and sPEP [i.e., from Day 35 (Groups 1) or Day 49 (Group 2) to Y1]
- Occurrence of pregnancies throughout the trial

6.1.9 Statistical Considerations & Statistical Analysis Plan

Study VAJ00001 was a hypothesis-testing clinical trial. Statistical methods provided in the protocol are presented here.

Reviewer Comment: Please see the statistical review for more information about the pre-specified statistical methods.

Hypothesis and hypothesis testing for the primary objective

The primary parameter was the difference of the percentage of subjects with an RVNA titer ≥ 0.5 IU/mL 14 days after the last vaccination of the PrEP regimen between the compared vaccine groups. The hypothesis tested was the following:

H_0: $P_{Group\ 1} - P_{Group\ 2} \leq -5\%$

H_1: $P_{Group\ 1} - P_{Group\ 2} > -5\%$

With P = percentage (%) of subjects with an RVNA titer ≥ 0.5 IU/mL 14 days after the last vaccination of the PrEP regimen

Group 1 (1-week, 2-dose regimen) was considered NI to Group 2 (3-dose regimen) if the hypothesis (H0) was rejected.

For the noninferiority hypothesis, the statistical methodology was based on the use of the 2-sided 95% confidence interval (CI) of the difference of percentages of subjects with an RVNA titer ≥ 0.5 IU/mL 14 days after the last vaccination of the PrEP regimen. The 95% CI for difference was calculated using the Wilson score method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 95% CI of the difference of the 2 percentages PGroup 1 - PGroup 2 was > -5%.

Reviewer Comment: The criterion for NI is acceptable from the clinical perspective. Please see the statistical review for a detailed discussion of the acceptability of the methodology for analysis of the primary objective.

No acceptability criteria were established for any arm of the study (i.e., minimum percentage of participants with RVNA titer of ≥0.5 IU/mL by RFFIT 14 days after last PrEP vaccination); establishment of acceptability criteria would ensure a minimum percentage of participants reached the aforementioned RFFIT threshold to demonstrate sufficient evidence of inferred effectiveness.

Statistical methods for the secondary objectives

Hypothesis testing for the secondary objectives was not performed; analyses of these objectives were descriptive.

Analysis sets

The study included 3 main analysis sets:

- Full Analysis Set (FAS): Two FASs were defined.
  - The PrEP FAS consisted of the subset of randomized participants who received at least one dose of the study vaccines during the PrEP period.
  - The sPEP FAS consisted of those participants who received at least one dose of the study vaccines during the sPEP period.
- Per-Protocol Analysis Set (PPAS): Two PPASs were defined, the PrEP PPAS and the sPEP PPAS. If participants met one or more of the following criteria, they were eliminated from the PrEP or sPEP PPAS:
  - PrEP PPAS
    - Participant did not meet all inclusion criteria or met at least one exclusion criterion
    - Participant did not complete the vaccination schedule for the PrEP regimen
    - Participant received a vaccine other than the one that they were randomized to receive during the PrEP phase
    - Preparation or administration of the vaccine was not done as per protocol
    - Participant did not receive the vaccine during the pre-specified, allowable windows
    - Participant did not provide the baseline serology sample or the baseline serology sample did not provide a valid result (at Visit 1)
    - Participant did not provide the post-dose serology sample, did not provide the sample in the proper time window or the post-dose serology samples did not produce a valid result (at Visit 3 for Groups 1, 3, 4 and 5 or Visit 4 for Group 2)
    - Participant was seropositive at baseline (RVNA titer ≥LLOQ at baseline)

        - Participant received a protocol prohibited therapy during the PrEP regimen
    - sPEP PPAS
        - Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
        - Participant did not complete the vaccination schedule for the PrEP regimen and the sPEP regimen at Y1 (i.e., up to Visit 8)
        - Participant received a vaccine other than the one that he/she was randomized to receive during the PrEP regimen or the sPEP regimen at Y1 (i.e., up to Visit 8)
        - Preparation and/or administration of vaccine was not done as per-protocol during the PrEP regimen or the sPEP regimen at Y1 (i.e., up to Visit 8)
        - Participant did not receive vaccine in the protocol-defined time window during the PrEP regimen or the sPEP regimen at Y1.
        - Participant did not provide a post-dose serology sample following the sPEP regimen
        - Participant did not provide a post-dose serology sample in the pre-specified time window
        - Participant received a protocol-prohibited therapy during the sPEP regimen
- Safety Analysis Set (SafAS): Two SafASs were defined, and the safety of both sets were analyzed by vaccine received.
    - The PrEP SafAS consisted of participants who received at least 1 dose of study vaccine during the PrEP period.
    - The sPEP SafAS consisted of participants who received at least 1 dose of study vaccine during the sPEP period.

Reviewer Comment: The difference between the FAS and SafAS is that the FAS analysis considered the group the participant was randomized to and the SafAS considered the injection they received. As no participants were cross treated, these were essentially the same.

Sample size determination and power calculation

The sample size was driven by hypothesis testing of the NI objective. The Applicant chose a one-sided alpha level of 2.5% and a maximum clinically acceptable difference of −5% for the percentages of participants with an RVNA titer (by RFFIT) of ≥0.5 IU/mL at 14 days after the last PrEP vaccination of 2-dose compared with 3-dose groups. Assuming a percentage of 99% of participants in each group achieve that RVNA minimum threshold at the pre-specified timepoint and considering a randomization ratio of 2:1 for 2-dose and 3-dose groups, respectively, 193 and 97 evaluable participants in 2-dose and 3-dose groups, respectively would provide a power of approximately 90% to test the null hypothesis. Also, assuming 15% of participants will be non-evaluable, a total of 228 participants in 2-dose and 114 participants in 3-dose groups were planned for enrollment.

The Applicant stated that 228 participants in Group 1 (2-dose) would provide a probability of >89% of detecting any common AE with an incidence of at least 1%.

Missing data

Missing data were not imputed during immunogenicity analyses.

For safety analyses, the following methodology applied:

- Missing causality for unsolicited non-serious AEs and SAEs were considered for analysis purposes, related to vaccination
- For temperature missing a decimal point, the data were analyzed replacing the missing numeral after the decimal point with a zero
- Missing or partially missing start and stop dates for AEs remained missing and were not imputed
- For the recording of intensity, solicited reactions (except fever) with an investigator presence recorded as 'no' and with all daily records missing had daily intensities derived as "none"

Reviewer Comment: Please refer to Section 3.6.2.3.2.4 of the Clinical Study Report (CSR) and the Statistical Analysis Plan (SAP) for details.

Extreme values

If a value was < LLOQ, for analysis purposes, the Applicant used a computed value of LLOQ/2.

Reviewer Comment: Please refer to the statistical review and SAP for additional details about statistical methodology and analyses.

6.1.10 Study Population and Disposition

A total of 343 participants were enrolled in Groups 1 and 2 at two centers in the Philippines: 196 adults 18 years of age or older and 147 children between ages 2 to 17.

6.1.10.1 Populations Enrolled/Analyzed

Please see the Analysis Sets subheading under section 6.1.9 (Statistical Considerations and Statistical Analysis Plan) for a description of the analysis populations defined in the protocol.

The numbers and percentages of participants included in each study population in each study phase are presented below (Table 2).

Table 2. Evaluable Participants by Randomized Group and Analysis Set - Enrolled Participants

Analysis Set	2-dose group N=228 n (%)	3-dose group N=115 n (%)
PrEP FAS	228 (100)	115 (100)
PrEP SafAS	228 (100)	115 (100)
PrEP PPAS	209 (91.7)	109 (94.8)
sPEP FAS	200 (87.7)	107 (93.0)
sPEP SafAS	200 (87.7)	107 (93.0)
sPEP PPAS	192 (84.2)	99 (86.1)

Source: Adapted from 103931.5342/0 CSR Table 4.5, p. 92
Abbreviations: N=enrolled participants; n=percentage of participants fulfilling the item listed; sPEP=simulated PEP; FAS=full analysis set; SafAS=safety analysis set; PPAS=per-protocol analysis set.

PrEP phase

All randomized participants were included in the PrEP FAS as all randomized participants received at least one injection.

Reviewer Comment: One participant in 2-dose group withdrew, due to work relocation and did not receive the second injection, however this participant was still appropriately included in the SafAS.

The Applicant provided a tabular presentation of deviations that resulted in participant exclusion from the PPAS for the PrEP phase. Not included in Table 3 are potential additional reasons for exclusion from the PPAS; none of these reasons were reported for any group;

- Participant did not meet all inclusion criteria or met at least one exclusion criterion
- Participant received a vaccine other than what they were randomized to receive
- Preparation and/or administration of vaccine was not per protocol
- Participant did not provide baseline serology sample at Visit 1
- Participant did not provide post-dose serology sample in the proper time window
- Participant received a protocol-prohibited therapy during the PrEP regimen (up to Visit 3 for Groups 1 and 3 or Visit 4 for Group 2

Table 3. PrEP Phase Immunogenicity Analysis Sets by Imovax Rabies - Randomized Group – Randomized Participants

Analysis Set	2-dose Group N=228 n (%)	3-dose Group N=115 n (%)
PrEP FAS	228 (100)	115 (100)
PrEP PPAS	209 (91.7)	109 (94.8)
Participants with at least one deviation	19 (8.3)	6 (5.2)
Did not complete vaccination schedule	1 (0.4)	0 (0.0)
Invalid result for baseline serology sample	2 (0.9)	0 (0.0)
Participant seropositive at baseline[ϕ]	3 (1.3)	3 (2.6)
Post-dose serology sample not obtained[¥]	1 (0.4)	0 (0.0)
Invalid result for post-dose serology sample[¥]	13 (5.7)	3 (2.6)
Exposed to rabies virus during PrEP regimen	0 (0.0)	0 (0.0)

Source: Adapted from 103931.5342/0 CSR Table 4.3, pp. 85 – 86
Abbreviations: N=randomized participants; n=percentage of participants fulfilling the item listed (a participant could be associated with more than one deviation); PrEP=pre-exposure prophylaxis; FAS=full analysis set; PPAS=per-protocol analysis set
[ϕ] Seropositivity=RVNA titer ≥0.2 IU/mL by RFFIT at Visit 1
[¥] At Visit 3 for 2-dose group and Visit 4 for 3-dose group

No participants were excluded from the PrEP FAS as all randomized participants received at least one dose of vaccine.

A total of 19 (8.3%) in 2-dose and 6 (5.2%) in 3-dose group participants had at least 1 deviation leading to exclusion from the PrEP PPAS.

Reviewer Comment: Few deviations to scheduled vaccination and samplings were reported overall during the PrEP phase. The number of participants eligible for the PPAS in Groups 1 and 2 were sufficient for evaluation of the primary objective.

The percentage of participants that were seropositive at baseline (RVNA titer ≥0.2 IU/mL by RFFIT at Visit 1): 1.3% in 2-dose group and 2.6% in 3-dose group.

Reviewer Comment: Seropositivity in unvaccinated individuals has been reported in seroprevalence studies and at baseline evaluations in rabies vaccine studies in which previously vaccinated participants have been excluded (Gilbert 2012; Pichon 2022).

sPEP phase

The Applicant provided a table of deviations leading to exclusions to the PPAS for the sPEP phase:

Table 4. sPEP Phase Immunogenicity Analysis Sets – Randomized Participants

Analysis Set	2-dose Group N=228 n (%)	3-dose Group N=115 n (%)
PrEP FAS	228 (100)	115 (100)
Not vaccinated	28 (12.3)	8 (7.0)
sPEP FAS	200 (87.7)	107 (93.0)
sPEP PPAS	192 (84.2)	99 (86.1)
Participants with at least one deviation	36 (15.8)	16 (13.9)
Incomplete vaccination schedule (up to V08)	28 (12.3)	9 (7.8)
Did not receive vaccine in pre-specified time windowᵋ	1 (0.9)	0 (0.0)
Post-dose serology sample not obtained at V10	34 (14.9)	14 (12.2)
Post-dose serology sample not provided in pre-specified time window at V10	1 (0.4)	0 (0.0)
Invalid result for post-dose serology sample at V10	1 (0.4)	0 (0.0)
Participant received protocol-prohibited therapy from V07-V10	1 (0.4)	1 (0.9)

Source: Adapted from 103931.5342/0 CSR Table 4.4, p. 88
Abbreviations: N=randomized participants; n=percentage of participants fulfilling the item listed (a participant could be associated with more than one deviation); PrEP=pre-exposure prophylaxis; sPEP=simulated post-exposure prophylaxis; FAS=full analysis set; PPAS=per-protocol analysis set
ᵋ Did not receive vaccine in the pre-defined time windows during the PrEP regimen or did not receive vaccine at Y1/Visit 7 or did not receive vaccine in the proper time window at Visit 8

The following deviations were not reported in any group during the sPEP phase:

- Participant did not meet all protocol-specified inclusion criteria or met protocol-specified exclusion criteria
- Participant received a vaccine other than the one he/she was randomized to receive (up to V08)
- Participant was re-exposed to the rabies virus during the sPEP regimen

In total, of the 570 randomized participants, 56 (9.8%) were not vaccinated in the sPEP vaccination phase and thus were not included in the sPEP FAS. Of these 56 participants, 26 were discontinued prior to the PEP vaccination phase (2 during the PrEP vaccination phase and 24 between the PrEP and sPEP vaccination phases) and 30 participants who were present at V7/Y1 had at least one definitive contraindication to vaccination.

A total of 2 (0.4%) participants received protocol-prohibited medications during the sPEP vaccination phase: 1 (0.5%) participant in 2-dose group received equine RIG after Visit

8/Y1+3 days and 1 (0.9%) participant in Group 2 received tetanus immunoglobulin and tetanus toxoid vaccination after Visit 7/Y1.

Reviewer Comment: RIG is derived from pooled plasma samples of hyperimmunized human donors (human RIG; HRIG) or from horses (equine RIG; ERIG). Both preparations are considered equally potent and effective; however, only HRIG is recommended for use in the United States. Equine RIG is a less expensive but safe and effective alternative for RIG in some resource-limited settings.

The percentage of participants evaluable (i.e., for analyses of sPEP endpoints) was acceptable and not unexpected given the interval between the PrEP and sPEP phases.

The Applicant reports that in addition to the 56 randomized participants who were not vaccinated in the sPEP vaccination phase, deviations on scheduled samplings in the sPEP vaccination phase were mostly due to the COVID-19 pandemic. At Visit 10/Y1+14 days, a total of 16 (2.8%) randomized participants had onsite visit shifted to phone call visit and missed providing a blood sample due to travel restrictions. All vaccinated participants in the sPEP vaccination phase received their injections according to the planned administration route and site.

6.1.10.1.1 Demographics

Demographic characteristics of the study population of Groups 1 and 2 are presented below.

Table 5. Demographic Characteristics of the Study Population

Demographic	2-dose Group N=228 Sex, n (%) Age, years Age groups, n (%)	3-dose Group N=115 Sex, n (%) Age, years Age groups, n (%)
Sex	-	-
Male	115 (50.4)	48 (41.7)
Female	113 (49.6)	67 (58.3)
Age	-	-
Mean	22.5	24.1
Min/max	2.0, 52.0	2.0, 59.0
Median	21.0	22.0
Age groups	-	-
2 to 11	66 (28.9)	35 (30.4)
12 to 17	35 (15.4)	11 (9.6)
18 to 64	127 (55.7)	69 (60.0)
≥65	0 (0.0)	0 (0.0)

Source: Adapted from 103931.5342 Clinical Study Report, Table 4.6, p. 94
Abbreviations: max=maximum; min=minimum; n=percentage of participants fulfilling the item listed

Reviewer Comment: No adults ≥65 years of age were randomized into the study. Rabies PrEP in the U.S. is generally administered to people at risk of rabies from occupational exposure (e.g., rabies vaccine workers, veterinarians), recreational exposure (e.g., cavers), or travelers to endemic areas; it is expected that some U.S. citizens ≥60 years of age would be eligible for PrEP. Therefore, had CBER had the opportunity to review

the protocol, (b) (5)

As expected, the kinetics of the immune response to PrEP show variability. Limited information is available regarding whether advanced age is a predictive factor for late responses to PrEP vaccination, lower titers in response to vaccination or reduced durability of these responses at timepoints distant from vaccination.

Demographic breakdowns for race and/or ethnicity were not performed; all participants were from the Philippines.

Reviewer Comment: Historically, there has not been any substantial evidence of differences in safety or effectiveness of rabies vaccine among different racial and ethnic groups, the lack of such diversity in this study is not considered an issue with regard to broader applicability of the results of immunogenicity assessments.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Concomitant medications were reported up to V4/V5 in PrEP phase and from V7 to V11 in sPEP phase. Less than 1/6 of the participants reported concomitant medication use in the PrEP phase in each Groups 1 and 2. Fewer than 3% of participants reported reportable concomitant medications during the sPEP phase. No major differences in terms of concomitant medications were observed between groups in both the PrEP FAS and the simulated PEP FAS in VAJ00001 study.

6.1.10.1.3 Participant Disposition

As planned, 570 participants were enrolled in the study. Enrollment across the two study sites was unequal due to, as the Applicant stated, a “competitive participant enrollment strategy” but the randomization ratio was maintained at each study site.

Table 6 presents the disposition of participants in 2-dose and 3-dose groups by randomized group for the PrEP vaccination phase.

Table 6. Participant Disposition PrEP Vaccination Phase – Randomized Participants

Disposition	2-dose Group n (%)	3-dose Group n (%)
V01/D0	--	--
Randomized	228 (100)	115 (100)
Attended	228 (100)	115 (100)
Blood draw	228 (100)	115 (100)
Vaccinated	228 (100)	115 (100)
Discontinued	0 (0.0)	0 (0.0)
V02/D7	--	--
Attended	228 (100)	115 (100)
Vaccinated	227 (99.6)	115 (100)
Discontinued	1 (0.4)	0 (0.0)
VW not due to AE	1 (0.4)	0 (0.0)
V03/D21	--	--
Attended	227 (99.6)	115 (100)
Blood draw	227 (99.6)	NA
Vaccinated	NA	115 (100)

Disposition	2-dose Group n (%)	3-dose Group n (%)
V01/D0	--	--
Discontinued	0 (0.0)	0 (0.0)
V04/D35	--	--
Attended	227 (99.6)	115 (100)
Blood draw	NA	115 (100)
Discontinued	0 (0.0)	0 (0.0)
V05/D49	--	--
Attended	NA	115 (100)
Discontinued	NA	0 (0.0%)

Source: Adapted from 103931.5342, Clinical Study Report, Table 4.1, pp. 78-79
Abbreviations: AE=Adverse event; VW=Voluntary withdrawal.

Between PrEP and sPEP vaccination phase

Eleven participants in 2-dose group, 4 in 3-dose group were discontinued between the PrEP and the sPEP vaccination phase. The reasons for early terminations during this period were as follows:

- Voluntary withdrawal not due to an AE: 5 in 2-dose group, 4 in 3-dose group.
- Discontinued for non-compliance with protocol: 3 in 2-dose group.
- Lost to follow-up: 2 in 2-dose group.
- One participant in 2-dose group experienced a fatal SAE.

Reviewer Comment: Refer to section 6.1.12.3 of this memo for summary of the fatal SAE.

The following table (Table 7) presents the disposition by randomized groups in 2-dose group and 3-dose group for the sPEP vaccination phase.

Table 7. Participant Disposition sPEP Vaccination Phase – sPEP FAS

Disposition	2-dose Group n (%)	3-dose Group n (%)
V07/Y1	--	--
Attended	200 (100)	107 (100)
Blood draw	200 (100)	107 (100)
Vaccinated	200 (100)	107 (100)
V08/Y1+3D	--	--
Attended	200 (100)	107 (100)
Vaccinated	200 (100)	106 (99.1)
V09/Y1+7D	--	--
Attended	199 (99.5)	107 (100)
Blood draw	199 (99.5)	107 (100)
V010/Y1+14D	--	--
Attended	199 (99.5)	107 (100)
Blood draw	194 (97.0)	101 (94.4)
V11/Y1+31D	--	--
Attended	199 (99.5)	107 (100)
Discontinued	1 (0.5)	0 (0.0)
VW not due to AE	1 (0.5)	0 (0.0)

Source: Adapted from 103931.5342, Clinical Study Report, Table 4.2, p. 82
Abbreviations: AE=adverse event; VW=voluntary withdrawal

At V07/Y1, 514 participants were present, provided a blood sample and were vaccinated.

At V08/Y1+3D, all 514 participants were present and 2 of the 514 were not vaccinated; one participant in 3-dose group had received a protocol-prohibited therapy.

All participants but one in 2-dose group (who voluntarily withdrew not due to an AE) were present at V09, V10 and V11.

Reviewer Comment: The percentages of participants who participated in the FAS and PPAS for both phases of the study were adequate for the determination of safety and effectiveness, respectively.

6.1.11 Efficacy Analyses

The NI analysis was performed by comparing SCR between 2-dose and 3-dose PrEP vaccination regimens 14 days post last dose.

6.1.11.1 Analyses of Primary Endpoint(s)

The primary endpoint of the study was to assess percentage of participants with a RVNA titer ≥ 0.5 IU/mL as measured by RFFIT 14 days after the last PrEP regimen vaccination (D21 for Group 1; D35 for Group 2). The PPAS was the primary immunogenicity population for analysis of the primary endpoint and results from the FAS was supportive. Results from the PPAS and FAS are presented below.

Table 8. Noninferiority Test - Percentage of Participants With an RVNA titer ≥0.5 IU/mL 14 Days After Last Vaccination - PPAS and FAS

Analysis Set	2-dose Group n/M % SC (95% CI)	3-dose Group n/M % SC (95% CI)	2-dose Group – 3-dose Group % (95% CI)
PPAS RVNA titer ≥0.5 IU/mL	202/209 96.7% (93.2, 98.6)	109/109 100.0% (96.7, 100)	-3.349 (−6.751, 0.464)
FAS RVNA titer ≥0.5 IU/mL	207/214 96.7% (93.4, 98.7)	112/112 100% (96.8, 100)	-3.271 (−6.597, 0.445)

Source: Adapted from 103931.5342 CSR Tables 5.1 (p. 96) and 9.39 (p. 204)
Abbreviations: SC=seroconversion, titer ≥0.5 IU/mL by RFFIT; PPAS=Per Protocol Analysis Set; FAS=Full analysis set; n=number of participants reporting the endpoint; M=number of participants available for the relevant endpoint; CI=confidence interval; IU/mL=international units per milliliter; RVNA=rabies virus neutralization assay

The results failed to demonstrate the primary objective as the LL of the 95% CI of the difference in percentages of participants in the PPAS seroconverting 14 days after last vaccination was less than the pre-specified acceptable clinical margin of −5%.

Reviewer Comment: Statistical NI of the percentages of participants with a titer of 0.5 IU/mL 14 days after primary regimen completion in the 2-dose group as compared with the 3-dose group was not demonstrated. One hypothesis offered by the Sponsor for why the study failed to meet the NI endpoint is that the immunogenicity assessment was performed too soon at D21, (14 days after the last dose) versus the standard timeframe of 21 - 28 days after the last dose to allow for a peak immune response (please see

Section 10.1, Table 24 for the discussion on the study results with regard to licensure of a two-dose series). However, the study was not designed to assess additional timepoints; therefore, the definitive cause of the narrowly missed primary endpoint remains unknown.

6.1.11.2 Analyses of Secondary Endpoints

Immunogenicity evaluation of the PrEP regimen overall

Baseline (pre-dose 1) immunogenicity evaluations and immunogenicity results evaluated at 2 weeks after last vaccination in Groups 1 and 2 (D21 and D35, respectively) are presented below on the FAS and PPAS. As defined by the protocol, 100% of participants in the PPAS for both 2-dose and 3-dose groups had RVNA titers <0.2 IU/mL at baseline.

Table 9. Immunogenicity Evaluation Results – RVNA Titers (RFFIT Method in IU/mL) – D0 and D21 (2-dose Group) or 35 (3-dose Group) – PrEP FAS and PPAS

Event	2-dose Group FAS N=228 n (%) [95% CI]	2-dose Group PPAS N=209 n (%) [95%CI]	3-dose Group FAS N=115 n (%) [95% CI]	3-dose Group PPAS N=109 n (%) [95% CI]
Pre-Dose 1 (D0)	--	--	--	--
Available Data¥	226	209	115	109
Titer ≤0.2 IU/mL n (%)	223 (98.7%)	209 (100%)	112 (97.4%)	109 (100%)
Titer ≥0.5 IU/mL	1 (0.4) [0.0%, 2.4%]	0 (0.0%) [0.0%, 1.7%]	3 (2.6) [0.5%, 7.4%]	0 (0.0%) [0.0%, 3.3%]
Titers	-	-	-	-
GMT	0.102 [0.100, 0.105]	0.100 [NC]	0.109 [0.099, 0.121]	0.101 [0.100, 0.102]
D21/Grp 1 or D35/Grp 2	--	--	--	--
Available data¥	214	209	112	109
Titer ≤0.2 IU/mL n (%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
Titer ≥0.5 IU/mL	207 (96.7%) [93.4%, 98.7%]	202 (96.7%) [93.2%, 98.6%]	112 (100) [96.8%, 100%]	109 (100%) [96.7%, 100%]
Titers	-	-	-	-
GMT	3.18 [2.76, 3.67]	3.05 [2.65, 3.50]	12.6 [10.8, 14.7]	11.9 [10.3, 13.7]

Source: Adapted from 103931.5342 CSR Tables 5.2 (pp. 97 – 98) and Table 9.40 (pp. 205 – 208)
Abbreviations: GMT=Geometric mean titer; RVNA=rabies virus neutralizing antibody; D=Day; Grp=Group; RFFIT=Rapid Fluorescent Focus Inhibition Test; PrEP=pre-exposure prophylaxis; FAS=full analysis set; PPAS=Per-Protocol Analysis Set; CI=confidence interval; NC=non calculable; IU/mL=international units per milliliter
¥=Number of participants data available for the relevant endpoint
n=Number of participants experiencing the endpoint for the parameter

Baseline - At baseline, 3 participants each in 2-dose (1.3%) and 3-dose groups (2.6%) in the PrEP FAS had an RVNA titer of ≥0.2 IU/mL. Of these seropositive participants, 1 participant in 2-dose group (0.4%) and 3 in 3-dose group (2.6%) had baseline titers of ≥0.5 IU/mL. The highest baseline titer reported was that of a 46-year-old male in Group 2 with a baseline titer of 19.4 IU/mL.

Fourteen days after last vaccination (overall) - At 14 days after the last PrEP vaccination (D21 for 2-dose group and D35 for 3-dose group), 1 participant in the FAS of 2-dose group (0.5%) was seronegative (RVNA titer <0.2 IU/mL); all participants in 3-dose group

were seropositive. The participant in 2-dose group (a 42-year-old male) who remained seronegative at D21 after 2 doses had a robust response to sPEP at Y1+D10 (RVNA titer of 11.5).

All participants in the FAS of 3-dose group seroconverted (RVNA titer ≥0.5 IU/mL) at 14 days after last vaccination. Seven participants in 2-dose group, including the one participant who was not seropositive at 14 days after last vaccination, did not seroconvert. Of the 6 Group 1 (2-dose group) participants who were seropositive but had not seroconverted at the 14 day post last vaccination timepoint, 5 had an RVNA titers of 0.3 or 0.4 IU/mL. The participant in 2-dose group who was not seropositive at the 14 day post last vaccination timepoint had a robust response to sPEP.

Reviewer comment: One participant in Group 5 who was not seropositive following the primary series remained seronegative throughout the study. The participant was reported to have taken methylprednisolone for 5 days before Visit 10/Y1+14D, which does not explain the lack of seroconversion following the primary series and was thought unlikely to have affected a response to sPEP. However, the underlying condition that the participant was taking the steroid treatment for might have contributed to the lack of seroconversion.

Immunogenicity results 14 days after last vaccination from the PrEP PPAS were similar to those observed in the PrEP FAS.

Reviewer Comment: Geometric mean titers (GMTs) from 3-dose group were substantially higher at 14 days after the last vaccination as compared with 2-dose group.

Antibody persistence

Antibody persistence evaluations for 2-dose and 3-dose groups at D180 and Y1 are presented below.

Table 10. Immunogenicity Results – Numbers and Percentages of Participants With Specified RVNA Titers and GMTs at D180, FAS and PPAS

Event	2-dose Group FAS N=228 n (%) [95% CI]	2-dose Group PPAS N=209 n (%) [95% CI]	3-dose Group FAS N=115 n (%) [95% CI]	3-dose Group PPAS N=109 n (%) [95% CI]
Available data¥	216	199	105	99
Titer ≤0.2 IU/mL n (%)	61 (28.2%)	57 (28.6%)	12 (11.4%)	12 (12.1%)
Titer ≥0.2 IU/mL	155 (71.8%) [65.3%, 77.7%]	142 (71.4%) [64.5%, 77.5%]	93 (88.6%) [80.9%, 94.0%]	87 (87.9%) [79.8%, 93.6%]
Titer ≥0.5 IU/mL	99 (45.8%) [39.1%, 52.7%]	88 (44.2%) [37.2%, 51.4%]	58 (55.2%) [45.2%, 65.0%]	54 (54.5%) [44.2%, 64.6%]
GMT	0.443 [0.380, 0.516]	0.426 [0.364, 0.499]	0.695 [0.550, 0.880]	0.617 [0.504, 0.754]

Source: Adapted from 103931/5342 CSR Tables 5.3 (pp. 99-100) and Table 9.42 (p. 215)
Abbreviations: FAS=Full analysis set; GMT=geometric mean titer; PPAS=per protocol analysis set; N=number of participants in the FAS or PPS by group; n=number of participants experiencing the endpoint
¥=number of participants with available data for the relevant endpoint

The percentage of participants who were seronegative at D180 was numerically higher for 2-dose group as compared with 3-dose group. The percentage of seropositive

participants (RVNA titer ≥0.2 IU/mL) at D180 was numerically higher for 3-dose group as compared with 2-dose group, and CIs around the point estimates did not overlap. The percentage of seroconverted participants (RVNA titer ≥0.5 IU/mL) were numerically higher in 3-dose group as compared with 2-dose group at that timepoint, however, CIs around that percentage overlapped.

Reviewer Comment: The higher percentage of participants with an RVNA titer by RFFIT <0.2 IU/mL (seronegative participants) and lower percentages of seropositive and seroconverted in the 2-dose group as compared with the 3-dose group at D180 may have clinical implications for individuals at continuous risk for recognized and unrecognized rabies exposures e.g. these individuals may require more frequent titer checks and earlier booster dosing for titers <0.5 IU/mL than the current CDC recommended every 6 months surveillance.

Immunogenicity results at Y1 for Groups 1 and 2 (both FAS and PPAS) are presented below.

Table 11. Immunogenicity Results – Numbers and Percentages of Participants With Specified RVNA Titers and GMTs at Y1, PrEP FAS and PPAS

Event	2-dose Group FAS N=228 n (%) [95% CI]	2-dose Group PPAS N=209 n (%) [95% CI]	3-dose Group FAS N=115 n (%) [95% CI]	3-dose Group PPAS N=109 n (%) [95% CI]
Available data¥	211	194	110	104
Titer ≤0.2 IU/mL n (%)	45 (21.3%)	44 (22.7%)	15 (13.6%)	14 (13.5%)
Titer ≥0.2 IU/mL	166 (78.7%) [72.5%, 84.0%]	150 (77.3%) [70.8%, 83.0%]	95 (86.4%) [78.5%, 92.2%]	90 (86.5%) [78.4%, 92.4%]
Titer ≥0.5 IU/mL	122 (57.8%) [50.8%, 64.6%]	109 (56.2%) [48.9%, 63.3%]	69 (62.7%) [53.0%, 71.8%]	64 (61.5%) [51.5%, 70.9%]
GMT	0.607 [0.510, 0.723]	0.570 [0.478, 0.680]	0.769 [0.605, 0.979]	0.695 [0.557, 0.866]

Source: Adapted from 103931/5342 CSR Tables 5.3 (pp. 100 - 101) and Table 9.42 (p. 216)
N=number of participants in the FAS or PPS by group; n=number of participants experiencing the endpoint; FAS=full analysis set; PPAS=per-protocol analysis set; GMT=geometric mean titer; IU/mL=international units per milliliter.
¥=number of participants with available data for the relevant endpoint

Reviewer Comment: The within group point estimates of the percentages of seroconverted participants (RVNA titers ≥0.5 IU/mL) were higher for Y1 than for D180; but CIs around the point estimates overlapped. This suggests a "plateau" effect where RVNA titers decline through 6 months after completion of a PrEP series and plateau somewhere around the 6 month post-PrEP series timepoint.

SCRs were higher (in both the FAS and PPAS) for 3-dose group as compared with 2-dose group at D180 and Y1, but CIs overlapped. Comparing each analysis set between groups, GMTs were higher for 3-dose group at both timepoints as well; CIs for the GMTs overlapped at Y1, but not at D180.

Immunogenicity of the sPEP regimen

Immunogenicity results of the sPEP regimen from participants in 2-dose and 3-dose groups are presented below for the timepoints Y1, Y1+7D and Y1+14D.

Table 12. Immunogenicity Results – RVNA Titers by RFFIT- sPEP FAS and PPAS at Y1, Y1+7D and Y1+14D

Event	2-dose Group FAS N=200 n (%) [95% CI]	2-dose Group PPAS N=192 n (%) [95% CI]	3-dose Group FAS N=107 n (%) [95% CI]	3-dose Group PPAS N=99 n (%) [95% CI]
Y1	--	--	--	--
Available data¥	195	187	107	99
Titer ≤0.2 IU/mL n (%)	45 (23.1%)	44 (23.5%)	15 (14.0%)	15 (15.2%)
Titer ≥0.2 IU/mL	150 (76.9%) [70.4%, 82.6%]	143 (76.5%) [69.7%, 82.4%]	92 (86.0%) [77.9%, 91.9%]	84 (84.8%) [76.2%, 91.3%]
Titer ≥0.5 IU/mL	107 (54.9%) [47.6%, 62.0%]	102 (54.5%) [47.1%, 61.8%]	66 (61.7%) [51.8%, 70.9%]	60 (60.6%) [50.3%, 70.3%]
GMT	0.523 [0.447, 0.611]	0.518 [0.442. 0.608]	0.738 [0.580, 0.939]	0.711 [0.551, 0.917]
Y1+7D	--	--	--	--
Available data¥	198	191	106	98
Titer ≤0.2 IU/mL n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Titer ≥0.5 IU/mL	198 (100%) [98.2%, 100%]	191 (100%) [98.1%, 100%]	106 (100%) [96.6%, 100%]	98 (100%) [96.3%, 100%]
GMT	32.4 [27.4, 38.3]	32.9 [27.8, 39.0]	25.3 [20.9, 30.6]	24.8 [20.3, 30.2]
Y1+14D	--	--	--	--
Available data¥	193	192	101	99
Titer ≤0.2 IU/mL n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Titer ≥0.5 IU/mL	193 (100%) [98.1%, 100%]	192 (100%) [98.1%, 100%]	101 (100%) [96.4%, 100%]	99 (100%) [96.3%, 100%]
GMT	71.6 [61.2, 83.6]	72.1 [61.7, 84.2]	51.3 [43.5, 60.6]	51.1 [43.1, 60.5]

Source: Adapted from 103931/5342 CSR Tables 5.4 (pp. 102 - 103) and Table 9.44 (pp. 225 -227)
N=number of participants in the FAS or PPS by group; n=number of participants experiencing the endpoint; Y=year
¥=number of participants with available data for the relevant endpoint

Reviewer Comment: Following sPEP, one hundred percent of participants in both treatment groups had RVNA titers ≥0.5 IU/mL by RFFIT at Y1+7D and Y1+14D after 2 doses of Imovax Rabies administered on Days 0 and 3; both regimens adequately primed participants for rapid anamnestic responses following an sPEP regimen. The GMTs at Y1+14D appear higher in the 2-dose group compared with the 3-dose group. The reason for this difference is not clear; however, it is notable that either regimen induced a robust response that is well above the RVNA titer ≥0.5 IU/mL, indicative of vaccine-induced protection.

No data are available for evaluation of booster dosing (a single dose) of previously vaccinated individuals.

6.1.11.3 Subpopulation Analyses

The Applicant provided immunogenicity analyses by age class: 2-11 years of age, 12-17 years of age and 18-64 years of age.

Reviewer Comment: No participants ≥60 years of age were enrolled, but the age groups will be presented as defined.

Immunogenicity evaluation of the PrEP regimen by age group

The immunogenicity evaluations of the PrEP regimens for 2-dose and 3-dose groups by age class are presented below on the FAS.

Table 13. Immunogenicity Data – Pre-Vaccination and Two Weeks After Primary Regimen for FAS by Age Class

Event	2-dose Group 2-11 N=228 n (%) [95% CI]	2-dose Group 12-17 N=228 n (%) [95% CI]	2-dose Group 18-64 N=228 n (%) [95% CI]	3-dose Group 2-11 N=115 n (%) [95% CI]	3-dose Group 12-17 N=115 n (%) [95% CI]	3-dose Group 18-64 N=115 n (%) [95% CI]
Pre-Dose 1 (D0)	--	--	--	--	--	--
Available Data¥	65	35	126	35	11	69
Titer ≥0.5 IU/mL	0 (0.0) [0.0, 5.5]	1 (2.9) [0.1, 14.9]	0 (0.0) [0.0, 2.9]	1 (2.9) [0.1, 14.9]	1 (9.1) [0.2, 41.3]	1 (1.4) [0.0, 7.8]
GMT	0.101 [0.099, 0.102]	0.107 [0.094, 0.121]	0.102 [0.099, 0.105]	.109 [0.094, 0.127]	0.116 [0.084, 0.160]	0.108 [0.093, 0.126]
D21/Grp 1 or D35/Grp 2	--	--	--	--	--	--
Available data¥	63	34	117	34	9	69
Titer ≤0.2 IU/mL n (%)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Titer ≥0.5 IU/mL	63 (100) [94.3, 100]	34 (100) [89.7,100]	110 (94.0) [88.1, 97.6]	34 (100) [89.7, 100]	9 (100) [66.4, 100]	69 (100) [94.8,100]
GMT	4.70 [3.90, 5.67]	3.79 [2.72, 5.28]	2.45 [1.98, 3.02]	16.3 [12.8, 20.6]	14.7 [7.73, 28.0]	10.9 [8.79, 13.4]

Source: Adapted from 103931.5342, Appendix 15, Table 2, pp. 19 – 31
N=number of participants in the group; N=number of participants in the group experiencing that endpoint;
IU/mL=International units per milliliter; GMT=Geometric mean titer; CI=confidence interval.
¥=number of participants in the group with data available for the relevant endpoint

The within group point estimates of the GMTs two weeks after last vaccination decreased slightly with advancing age. GMTs in 3-dose Group were significantly higher two weeks after last vaccination as compared with 2-dose group. One hundred percent of children in both pediatric age classes for both treatment groups seroconverted two weeks after last vaccination (although not presented here, 100% of children seroconverted in the other treatment groups as well).

Antibody persistence evaluation of the PrEP regimen by age group

Immunogenicity of the sPEP regimen

Immunogenicity results on Y1 prior to initiation of sPEP and on Days 7 and 14 after sPEP by age class are present below on the FAS.

Table 14. Immunogenicity Data – Pre- and Post sPEP, FAS by Age Class

Event	2-dose Group 2-11 N=200 n (%) [95% CI]	2-dose Group 12-17 N=200 n (%) [95% CI]	2-dose Group 18-64 N=200 n (%) [95% CI]	3-dose Group 2-11 N=107 n (%) [95% CI]	3-dose Group 12-17 N=107 n (%) [95% CI]	3-dose Group 18-64 N=107 n (%) [95% CI]
Year 1	--	--	--	--	--	--
Available Data¥	59	34	102	34	10	63
Titer ≤0.2 IU/mL n (%)	3 (5.1)	6 (17.6)	36 (35.3)	0 (0.0)	2 (20.0)	13 (20.6)
Titer ≥0.2 IU/mL	56 (94.9) [85.9, 98.9]	28 (82.4) [65.5, 93.2]	66 (64.7) [54.6, 73.9]	34 (100) [89.7, 100]	8 (80.0) [44.4, 97.5]	50 (79.4) [67.3, 88.5]
Titer ≥0.5 IU/mL	46 (78.0) [65.3, 87.7]	20 (58.8) [40.7, 75.4]	41 (40.2) [30.6, 50.4]	31 (91.2) [76.3, 98.1]	6 (60.0) [26.2, 87.8]	29 (46.0) [33.4, 59.1]
GMT	0.791 [0.651, 0.960]	0.688 [0.438, 1.08]	0.375 [0.302, 0.467]	1.43 [1.02, 2.01]	0.758 [0.272, 2.12]	0.514 [0.377, 0.701]
Y1+7D	--	--	--	--	--	--
Available data¥	60	35	103	34	10	62
Titer ≤0.2 IU/mL n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Titer ≥0.5 IU/mL	60 (100) [94.0,100]	35 (100) [90.0, 100]	103 (100) [96.5, 100]	34 (100) [89.7,100]	10 (100) [69.2, 100]	62 (100) [94.2, 100]
GMT	46.6 [36.2, 60]	44.0 [29.6, 65.5]	23.6 [18.6, 30.1]	51.6 [37.6,70.8]	22.8 [14.2,36.4]	17.4 [14.0, 21.6]
Y1+14D	--	--	--	--	--	--
Available Data¥	60	32	101	32	9	60
Titer ≤0.2 IU/mL n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Titer ≥0.5 IU/mL	60 (100) [94.0, 100]	32 (100) [89.1, 100]	101 (100) [96.4, 100]	32 (100) [89.1, 100]	9 (100) [66.4, 100]	60 (100) [94.0, 100]
GMT	77.3 [60.8,98.2]	89.2 [59.0,135]	63.7 [50.6, 80.3]	70.0 [51.3,95.7]	38.3 [23.8, 61.6]	45.4 [36.7, 56.2]

Source: Adapted from 103931.5342, Appendix 15, Table 4, pp. 48 - 61
Abbreviations: GMT=geometric mean titer; CI=confidence interval; N=number of participants of all ages in the group; n=number of participants in the group experiencing that endpoint; Y=year
¥=number of participants in the group with data available for the relevant endpoint

Reviewer Comment: Responses to sPEP were robust in both treatment groups and all age groups. GMTs appeared to rise from Y1 + 7D to Y1 + 14D and were higher in children than in adults.

6.1.11.4 Dropouts and/or Discontinuations

Please refer to section 6.1.10.1.3.

6.1.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.1.12 Safety Analyses

As the primary comparison for safety and effectiveness is between Groups 1 and 2, which differed only in the number of administrations of the same vaccine (Imovax Rabies) by the same route (IM), the review of the safety data focused mainly on evaluation of any unusual AEs not previously enumerated in the product package insert.

6.1.12.1 Methods

See sections 6.1.2 and 6.1.7.

6.1.12.2 Overview of Adverse Events

Overview of safety: PrEP phase

Overall safety for treatment Groups 1 (2-dose) and 2 (3-dose) is presented below on the SafAS during the PrEP vaccination phase. During the PrEP vaccination phase, unsolicited events, AEs leading to withdrawal and SAEs were collected up to 28 days after last injection (D35 for 2-dose group and D49 for 3-dose group); injection site and systemic reactions were collected within 7 days of any injection. No immediate AEs or reactions (within 30 minutes after any injection) were reported in either group (or for any of the five treatment groups).

Table 15. Overview of Safety, PrEP Vaccination Phase, SafAS

Participants Reporting ≥1	**2-dose Group N=228 n/M % (95% CI)**	**3-dose Group N=115 n/M % (95% CI)**
Solicited reaction	92/228 40.4 (33.9, 47.0)	58/115 50.4 (41.0, 59.9)
Solicited IS reaction	72/228 31.6 (25.6, 38.0)	43/115 37.4 (28.5, 46.9)
Solicited systemic reaction	64/228 28.1 (22.3, 34.4)	41/115 35.7 (26.9, 45.1)
Unsolicited AE	29/228 12.7 (8.7, 17.8)	22/115 19.1 (12.4, 27.5)
Unsolicited AR	5/228 2.2 (0.7, 5.0)	1/115 0.9 (0.0, 4.7)
AEs leading to study discontinuation	0/228 0.0 (0.0, 1.6)	0/115 0.0 (0.0, 3.2)
SAE	0/228 0.0 (0.0, 1.6)	0/115 0.0 (0.0, 3.2)
Related SAE	0/228 0.0 (0.0, 1.6)	0/115 0.0 (0.0, 3.2)
Death	0/228 0.0 (0.0, 1.6)	0/115 0.0 (0.0, 3.2)

Source: Adapted from 103931.5342, CSR Table 6.1, pages 108- 109
Abbreviations: N=numbers of participants in the SafAS; n=numbers of participants reporting the endpoint in the relevant row; M=number of participants with data available for the relevant endpoint; IS=Injection site; AE= Adverse event: AR=Adverse reaction; SAE=Serious adverse event.

All unsolicited AEs and ARs in Table 15 were non-serious. The rates of AEs reported were generally similar between groups (CIs overlapped); point estimates were slightly higher in 3-dose group, as compared with 2-dose group.

Overview of safety: between PrEP and sPEP phase

Related SAEs, life threatening SAEs and deaths were collected from D35/Visit 4 for 2-dose group, and D49/Visit 5 for 3-dose group until Y1/Visit 7.

One death (see section 6.1.12.3), judged unrelated to study vaccine was reported during this period. No other deaths or related or life-threatening SAEs were reported during this period.

Overview of safety: sPEP phase

The overview of safety during the sPEP phase is presented on the SafAS for Groups 1 and 2 below. During the sPEP vaccination phase, unsolicited events, AEs leading to withdrawal from the study and SAEs were collected up to 28 days after last injection; injection site and systemic reactions were collected within 7 days of any injection. No immediate AEs or reactions (within 30 minutes after any injection) were reported in either group (or for any of the five treatment groups).

Table 16. Overview of Safety, sPEP Vaccination Phase, SafAS

Participants Reporting ≥1	**2-dose Group N=200 n/M % (95% CI)**	**3-dose Group N=107 n/M % (95% CI)**
Solicited reaction	52/200 26.0 (20.1, 32.7)	23/107 21.5 (14.1, 30.5)
Solicited IS reaction	38/200 19.0 (13.8, 25.1)	21/107 19.6 (12.6, 28.4)
Solicited systemic reaction	32/200 16.0 (11.2, 21.8)	13/107 12.1 (6.6, 19.9)
Unsolicited AE	3/200 1.5 (0.3, 4.3)	1/107 0.9 (0.0, 5.1)
Unsolicited AR	0/200 0.0 (0.0, 1.8)	0/107 0.0 (0.0, 3.4)
AEs leading to study discontinuation	0/200 0.0 (0.0, 1.8)	0/107 0.0 (0.0, 3.4)
SAE	0/200 0.0 (0.0, 1.8)	0/107 0.0 (0.0, 3.4)
Related SAE	0/200 0.0 (0.0, 1.8)	0/107 0.0 (0.0, 3.4)
Death	0/200 0.0 (0.0, 1.8)	0/107 0.0 (0.0, 3.4)

Source: Adapted from 103931.5342/0, CSR Table 6.2, pages 112 - 113
Abbreviations: N=numbers of participants in the SafAS; n=numbers of participants reporting the endpoint in the relevant row; M=number of participants with data available for the relevant endpoint; ; IS=Injection site; AE= Adverse event: AR=Adverse reaction; SAE=Serious adverse event..

All unsolicited AEs in Table 16 were non-serious. No unsolicited ARs were reported. The rates of AEs reported were generally similar between groups (CIs overlapped).

6.1.12.3 Deaths

No deaths were reported during the PrEP vaccination phase (up to 28 days after last PrEP vaccination) or during the sPEP vaccination phase. One participant, a 2-year-old male in 2-dose group, died 190 days after his second IM injection of Imovax Rabies. Five days prior to his death, the child, who had no significant past medical history, was seen by a physician for a persistent fever, cough, conjunctivitis and a descending maculopapular rash. He was diagnosed with measles. He was admitted to the hospital on the day of his death and the final diagnosis was pneumonia. The cause of death on the death certificate was sepsis and community acquired pneumonia. The investigator considered the event unrelated to study vaccination.

Reviewer Comment: This reviewer concurs with the investigator's assessment of unrelated based on the information provided.

6.1.12.4 Nonfatal Serious Adverse Events

No SAEs were reported during the PrEP vaccination phase (within 28 days of last vaccination) or during the sPEP vaccination phase. From the end of the PrEP vaccination phase to the sPEP phase, only fatal and life-threatening SAEs were recorded.

Six pregnancies were reported in the 2-dose group and 3 in the 3-dose group. All pregnancies were reported between the PrEP vaccination phase and the simulated PEP vaccination phase. Two SAEs were reported as related to pregnancy, both occurring in Group 2 (3-dose Imovax Rabies IM PrEP regimen).

- A 41-year-old female with a history of hypertension had a last menstrual period (LMP) 72 days after the third Imovax Rabies injection. She reported abdominal pain on 201 days after her LMP (and 273 days after the third Imovax Rabies injection), and bleeding one day later. She was admitted to the hospital at 28 weeks gestation and gave birth vaginally on the same day to a stillborn female fetus. Cause of death was listed as "late fetal death due to prematurity".
- A 38-year-old female in Group 2, with no relevant medical history received 3 IM doses of Imovax Rabies and reported the LMP 269 days after her third dose of Imovax Rabies. The participants reported vaginal spotting 78 days after her LMP, followed by vaginal bleeding 4 days later. Examination revealed no fetal heartbeat 87 days after the LMP. A spontaneous abortion occurred at 15 weeks gestation 105 days after the LMP and 374 days after the third Imovax Rabies dose.

Both events were assessed by the investigator as unrelated to study product.

Reviewer Comment: This reviewer thinks that the investigator's assessment is reasonable. The medical history of hypertension summarized in the case narrative could not be confirmed in the medical history (MH) dataset. However, based on review of the case narrative above, the presence or absence of hypertension likely did not influence the outcome. Please see section 9.1.1 for additional information about pregnancies that were recorded during the study.

6.1.12.5 Adverse Events of Special Interest (AESIs)

AESIs were not collected.

6.1.12.6 Clinical Test Results

Clinical laboratory evaluations were not performed in this study.

6.1.12.7 Dropouts and/or Discontinuations

A total of 28 (4.9%) participants terminated the study early (2 participants during the PrEP vaccination phase, 24 participants between PrEP and sPEP vaccination phases, and 2 participants during the sPEP vaccination phase [including 1 participant not in the sPEP FAS]): 14 (6.1%) participants in Group 1, 4 (3.5%) participants in Group 2, 4 (5.2%) participants in Group 3, 4 (5.3%) participants in Group 4, and 2 (2.7%) participants in Group 5.

The reasons for early terminations during the full study were as follows:

- 17 (3.0%) voluntarily withdrew (not for an AE): 7 (3.1%) in Group 1, 4 (3.5%) in Group 2, 2 (2.6%) in Group 3, 2 (2.7%) in Group 4, and 2 (2.7%) in Group 5
- 7 (1.2%) participants were discontinued for non-compliance with protocol: 4 (1.8%) in Group 1, 2 (2.6%) in Group 3, and 1 (1.3%) in Group 4
- 3 (0.5%) were lost to follow-up: 2 (0.9%) in Group 1 and 1 (1.3%) in Group 4
- 1 (0.2%) participant experienced a fatal SAE: 1 (0.4%) in Group 1

Reviewer comment: For participants who were lost to follow-up or voluntarily withdrew from the study, this reviewer examined the available data and found no evidence supporting a temporal relationship between any adverse events and the study intervention.

6.1.13 Study Summary and Conclusions

Study VAJ00001 was a Phase 3, open-label, randomized, controlled multi-center study conducted in the Philippines to evaluate the immunogenicity and safety of 1-site IM and 2-site ID “2-dose” PrEP regimens (given at D0 and D7), followed by an sPEP regimen 1 year later (at D0 and D3) administered by the same route as the one used in the prior PrEP regimen. Participants received either Imovax Rabies or Verorab. Immunogenicity data at D21 (i.e., 14 days after 2nd dose), D35 (i.e., 21 days after 3rd dose), D180 (i.e., 180 days after last PrEP dose), year (Y)1 (i.e., 1 year after last PrEP dose and before booster dose), Y1+7 days (i.e., 7 days after booster dose), and Y1+14 days (i.e., 14 days after booster dose) are available in both pediatric and adult populations.

Immunogenicity Summary and Conclusion

Study VAJ00001 did not meet its pre-defined NI endpoint. One hypothesis offered by the Sponsor for why the study failed to meet the NI endpoint is that the immunogenicity assessment was performed too soon at D21, (D14 post last dose) versus the standard timeframe of 21 - 28 days post last dose to allow for a peak immune response. However, the study was not designed to assess additional timepoints; therefore, the definitive cause of the narrowly missed primary endpoint remains unknown. Following sPEP, 100% of participants developed a robust immune response, as measured by RVNA titers. The universal response to sPEP among participants demonstrates that PrEP was effective in priming participants to induce a robust anamnestic immune response, hence achieving its purpose.

Safety Summary and Conclusion

As expected, 2-dose Imovax Rabies series was well tolerated as compared with the 3-dose series with overall fewer reports of both local and systemic solicited adverse events in PrEP vaccination phase. In the sPEP vaccination phase, percentage of participants who reported solicited reactions was higher in 2-dose, compared with 3-dose group (26% of participants in the 2-dose group and 21.5% of participants in the 3-dose group). While local solicited AEs were comparable between 2-dose and 3-dose groups, solicited systemic reactions were reported in more participants in the 2-dose group (16% of participants in the 2-dose group and 12.1% of participants in the 3-dose group). The reason for this difference is not clear, but could be related to multiple factors, such as differences in study populations, vs different immune system priming after 2-dose compared with 3-dose regimen, or methodological factors, such as reporting bias.

The Applicant did not report any related SAEs during the trial. One unrelated fatal SAE of measles complicated by pneumonia and sepsis was reported in a 2-year-old male from the 2-dose Imovax Rabies group 190 days after his second injection of Imovax Rabies.

Overall, the data submitted did not raise safety concerns.

6.2 Trial #2

Study VRV12 was a Phase 3 study evaluating immunogenicity and safety of a Purified Vero Rabies Vaccine – Serum Free (VRVg) in comparison with Verorab and Imovax Rabies, in a PrEP regimen in both pediatric and adult populations and single booster dose of VRVg Administered at 1 Year post-3-dose primary series, and between 2 up to 3 years post-one week 2-dose primary series in a subset of adults in Thailand.

Reviewer comment: This memo discusses only the study design elements, objectives and endpoints relevant to this sBLA intended to support the safety and effectiveness of the 2-dose Imovax Rabies PrEP regimen. Because the interim CSR presents data up to the end of the 6-month safety follow-up after the Booster Phase in Cohort 1 and up to 28 days after the Primary Series in Cohort 2, no data regarding a booster dose after the 2-dose Imovax Rabies PrEP regimen were included.

6.2.1 Objectives (Primary, Secondary, etc.)

Immunogenicity of the PrEP regimen

Secondary objective #5: To demonstrate that 2-dose Imovax Rabies regiman at D28 was NI to 3-dose Imovax Rabies regimen at D42 in the overall participants (pooled pediatric and adult participants) in Cohort 1, in terms of percentage of participants achieving an RVNA titer ≥0.5 IU/mL, only if the 4th secondary immunogenicity objective was achieved.

Secondary objective #6: Description of immune response induced by Imovax Rabies at D28 (i.e., 21 days after the 2nd injection) and at D42 (i.e., 14 days after the 3rd injection) in all age groups (pediatric and adult populations).

Reviewer comment: Study VRV12 was already ongoing when the 5th and 6th secondary objectives were added to compare immune responses induced by 2-dose Imvoax Rabies regimen with 3-dose regimen. Hence the difference between time elapsed after the 2nd and 3rd vaccination doses and blood draws for immunogenicity assessment (21

days after 2nd injection and 14 days after 3rd injection). In this reviewer's opinion difference in timing of the blood draw after the 2nd and 3rd vaccinations should not affect overall NI conclusion, given the fact that NI is based on percentage of participants achieving an RVNA titer ≥0.5 IU/mL, not absolute RVNA titer values.

Safety

Secondary safety objectives included describing the safety profile of VRVg-2 versus Verorab and Imovax Rabies vaccines, as well as describing the safety of VRVg-2 booster vaccine.

Reviewer Comment: Only the 5th and 6th secondary immunogenicity objectives are relevant to this sBLA and will be discussed below. The study has a primary immunogenicity objective and a number of secondary immunogenicity objectives that need to be met sequentially. The primary as well as the first three secondary immunogenicity objectives were met and the 4th secondary immunogenicity objective was considered met from the clinical standpoint (b) (4) *). The primary as well as the 4 secondary objectives are not discussed in the memo as they were not related to the primary purpose of this sBLA, comparing the 2-dose and 3-dose PrEP regimens of Imovax Rabies. Safety objectives were descriptive and will be presented as such for Imovax Rabies vaccine only, as neither Verorab nor VRVg-2 is licensed in the U.S.*

6.2.2 Design Overview

This was a randomized, observer blind, controlled, multi-center study to evaluate immunogenicity and safety of a pre-exposure prophylaxis regimen of Purified Vero Rabies Vaccine-serum free (hence forth referred to as VRVg-2) as compared with Verorab and Imovax Rabies, in both pediatric and adult populations.

Reviewer Comment: The study also included a booster sub-study that was not submitted for consideration as part of this sBLA. Hence, the design of the booster study and its follow-up plan are not outlined in this review.

A total of 1700 healthy participants were planned for 3:1:1 randomization into the following groups at study entry to receive a primary regimen:

Table 17: Distribution of Subjects According to Vaccination Group.

Group	Vaccine	Number of adult participants	Number of pediatric participants
Group 1	VRVg-2	303	303
Group 2	Verorab	101	101
Group 3	Imovax Rabies	101	101
Group 4	VRVg-2	414	NA
Group 5	Verorab	138	NA
Group 6	Imovax Rabies	138	NA

Groups 1, 2 and 3 were part of Cohort 1, and Groups 4, 5 and 6 were part of Cohort 2. Pediatric and adult participants in Cohort 1 received a 3-dose PrEP schedule of VRVg-2 (Group 1), Verorab vaccine (Group 2) or Imovax Rabies vaccine (Group 3), at days 0, 7 and 28. Adult participants in Cohort 2 received a one week 2-dose schedule PrEP regimen of either VRVg-2 (Group 4), Verorab vaccine (Group 5) or Imovax Rabies vaccine (Group 6) at days 0 and 7.

Reviewer Comment: Study VRV12 was initially designed to demonstrate that VRVg-2 was NI to Verorab and to Imovax Rabies vaccines in each age group (pediatric and adult populations) when administered as a 3-dose PrEP regimen (Cohort 1). Most of the study objectives and endpoints are related to this goal. However, the Applicant amended the protocol to add a secondary objective to demonstrate NI of a 2-dose Imovax Rabies PrEP regimen versus a 3-dose Imovax Rabies PrEP regimen in the pooled population of Cohort 1, Group 3 participants (pediatric and adult), with a NI margin of −10%. CBER advised that it would consider the more stringent NI margin of −5% important in supporting effectiveness.

Cohort 1, Group 3 is the key group that contributes data to the NI analysis between 2-dose and 3-dose Imovax Rabies PrEP regimens (secondary immunogenicity objective #5). Cohort 2, Group 6 only contributes data to descriptive immunogenicity analysis (secondary immunogenicity objective #6) and safety analysis.

The study was conducted at 4 centers in Thailand, with five Principal Investigators: Terapong Tantawichien, M.D., Piroon Mootsikapun, M.D., Pope Kosalaraksa, M.D., Kulkanya Chokephaibulkit, M.D. and Sasisopin Kiertiburanakul, M.D.

The study was initiated on October 21, 2019. The date of the interim report submitted to FDA for review was February 27, 2023 (last participant last D35 visit from Cohort 2), with analyses based on a database lock date of August 23, 2023.

6.2.3 Population

Inclusion criteria (all criteria must have been met to qualify for study enrollment)

- ≥1 years of age on the day of inclusion
- ICF signed and dated by the participant and/or parent(s) or LAR and by an independent witness (if required by local regulations), as necessary; and Assent form signed and dated by the participant, as required.
- Participant (adult ≥18 years) or participant and parent/LAR (1 year to <18 years) able to attend all scheduled visits and to comply with all study procedures.

Select exclusion criteria

- Participant is pregnant, or lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to the 1st vaccination until 1 month after each vaccination. To be considered of non-childbearing potential, a female must be pre-menarche or post-menopausal for at least 1 year, or surgically sterile.

- Participation at the time of study enrollment or, planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure.
- Previous vaccination against rabies (in pre- or post-exposure regimen) with either the study vaccines or another vaccine.
- Receipt of any vaccine in the 4 weeks (28 days) preceding the 1st study vaccination or planned receipt of any vaccine prior to V05 for pediatric participants and adult participants in Cohort 1, and prior to V04 for adult participants in Cohort 2.
- Bite by, or exposure to, a potentially rabid animal in the previous 6 months with or without PEP.
- Receipt of immune globulins, blood or blood-derived products in the past 3 months.
- Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months).

Reviewer Comment: The eligibility criteria were acceptable.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Study products included: VRVg, Verorab and Imovax Rabies administered IM. Only Imovax Rabies vaccine will be described here.

Imovax Rabies is a purified inactivated rabies vaccine prepared on human diploid cell cultures. Each dose contains:

- Powder:
  - Rabies Virus- Wistar Rabies Pitman Moore/WI 38 1503-3M strain: ≥2.5 IU
  - Human albumin: (b) (4) mg
- Diluent:
  - Water for injection: 1 mL

Each dose may contain undetectable traces of neomycin, used during vaccine production.

Volume of each IM dose was 1 mL.

6.2.5 Directions for Use

Injections were administered to the deltoid (or anterolateral thigh for toddlers) area. Instructions were given to alternate arms for IM administrations or inject at least 3 cm apart from the previous injection site.

Please see the Imovax Rabies PI for additional instructions about product administration.

6.2.6 Sites and Centers

The study was conducted at 4 study centers in Thailand.

6.2.7 Surveillance/Monitoring

The study included 5 visits in Primary Series Cohort 1 on Days 0, 7, 28, 42 and 56 with a M7 phone call. Four visits were in Primary Series Cohort 2 on Days 0, 7, 28 and 35 with a M6 phone call.

All participants from Primary Series Cohort 1 had 3 scheduled blood samples on D0 (baseline), D28 (21 days after the 2nd dose) and D42 (14 days after the 3rd dose). All participants from Primary Series Cohort 2 had 2 scheduled blood samples on D0 (baseline) and D28 (21 days after the 2nd dose). In addition, adult participants from both cohorts who also participated in the booster phase would have additional blood draws.

Safety assessment included collection of specific AEs during pre-specified time intervals and recorded in a diary card.

- Unsolicited systemic AEs occurring 30 minutes following administration of each vaccine dose.
- Solicited injection site and systemic AEs occurring within 7 days after each injection.
- Unsolicited injection site and systemic AEs occurring between each injection and up to 28 days after each injection.

Pediatric participants and adult participants in Primary Series Cohort 1 recorded safety information in a Memory Aid from D56 (28 days following the 3rd injection) until M7 for the participants not involved in the booster phase, and until M12 for the adult subset in the Booster Phase Cohort 1. Adult participants in Primary Series Cohort 2 recorded safety information in the Memory Aid from D35 (28 days following the 2nd injection) until M6 (6-month safety follow-up after the last vaccination). Adult participants in the Immunogenicity Persistence and Booster Phase Cohort 2 subset recorded safety information leading up to the booster vaccination and afterwards (6-month safety follow-up after the booster vaccination).

- SAEs, AESIs and pregnancies were recorded for at least 6 months after each vaccination as applicable to Cohort 1 and Cohort 2.
    - The following AESIs were considered as SAEs and reported to the Applicant: anaphylactic reactions, encephalitis, and convulsions. These AESIs have been defined based on existing postmarketing safety data of other rabies vaccines.

AEs were graded as Grade 1-3 in intensity, and an investigator assessed the causal relationship between the AE and the investigational product as either “not related” or “related.”

Participants that permanently terminated the study because of an AE or a protocol deviation were to complete all scheduled safety follow-ups. If the participant’s status at the end of the study is “Withdrawal by Participant or Parent / Guardian / LAR”, the site would attempt to contact them for the 6-month follow-up except if they specified that they do not want to be contacted again.

The study was overseen by an internal Safety Management Team (SMT) who performed regular safety review in a blinded manner. The study did not include an Independent Data Monitoring Committee (IDMC) as the Applicant considered it unnecessary given

extensive experience with the study products, and the fact that one of the study products (VRVg) (b) (4) .

6.2.8 Endpoints and Criteria for Study Success

Secondary immunogenicity endpoint

RVNA titers (IU/mL) measured by RFFIT, summarized at the participant/ timepoint level.

Reviewer Comment: The primary immunogenicity objective and related endpoint as well as most secondary immunogenicity objectives and related endpoints are not applicable to the proposed USPI revisions based on this sBLA. The fifth secondary immunogenicity objective and related endpoints are presented for Cohort 1, Group 3 (3-dose group) and reviewed further in relevant sections below.

Secondary safety endpoints

This study did not have a primary safety endpoint. Secondary safety endpoints are listed below:

- Occurrence of any unsolicited systemic AEs reported in the 30 minutes after each vaccine injection
- Occurrence of solicited (pre-listed in the participant's diary card and eCRF) injection site and systemic reactions occurring within 7 days after each injection
- Occurrence of unsolicited injection site reactions occurring within 28 days after each injection and unsolicited systemic AEs up to 28 days after each injection
- Occurrence of SAEs and AESIs within at least 6 months after each vaccination as applicable to Cohort 1 and Cohort 2.
- SAEs (including AESIs) reported throughout the study

6.2.9 Statistical Considerations & Statistical Analysis Plan

No changes were made to the planned analyses after the finalization of the SAP. The SAP was finalized prior to clinical database lock (to include data up to and including last participant's last in-clinic visit).

For primary and key secondary immunogenicity objectives, the PPAS was used as the primary analysis set, and supplementary analysis was performed on FAS and/or FAS for immunogenicity (FASI), if necessary. For safety objectives, the SafAS was used.

The safety analysis will be performed on the SafAS, and the participants will be analyzed according to the vaccine they actually received in the primary series. Secondary safety endpoints were described by age group and vaccine group using descriptive statistical methods, without hypothesis testing.

NI testing of 2-dose Imovax Rabies at D28 versus 3-dose Imovax Rabies at D42

Only if the 4th secondary objective was achieved, then the 5th secondary NI objective would be tested with the following hypothesis Imovax Rabies group in overall participants (pooled pediatric and adult participants) in Cohort 1 only:

H0: PImovax Rabies at D28 (Group 3) - PImovax Rabies at D42 (Group 3) ≤ −10%
H1: PImovax Rabies at D28 (Group 3) - PImovax Rabies at D42 (Group 3) > −10%

With PImovax Rabies at D28 = percentage (%) of participants with an RVNA titer ≥0.5 IU/mL at D28 for Imovax Rabies in Cohort 1, and PImovax Rabies at D42 = percentage (%) of participants with an RVNA titer ≥0.5 IU/mL at D42 for Imovax Rabies in Cohort 1.

Reviewer Comment: In this study, the secondary hypothesis testing was only considered if the primary objective was met, and then secondary objectives were evaluated sequentially following a fixed-sequence method. However, the primary objective, as well as preceding secondary objectives are not relevant to and related to this sBLA, and hence will not be discussed in detail in this review except noting that the primary as well as the first 3 secondary objectives were met. The 4th secondary objective (b) (4) *; however, this objective was related to VRVg and did not impact the 2-dose vs 3-dose Imovax Rabies evaluation.*

As noted above, we did not agree that −10% NI margin was acceptable for the vaccine that is used for prevention of Rabies infection that has a near 100% mortality rate. The Applicant chose to proceed with −10% NI margin at their own risk; however, in the SAP the Applicant also included a "pre-specified" (i.e., before database lock) supplementary analysis based on NI margin of -5%.

6.2.10 Study Population and Disposition

Of the total 1708 enrolled participants, 100 adult (≥18 years old) and 100 pediatric (between ages ≥1 and <18 years) participants were randomized to Cohort 1, Group 3 (3-dose Imovax Rabies group) and 139 adult participants were randomized to Cohort 2, Group 6 (2-dose Imovax Rabies group).

6.2.10.1 Populations Enrolled/Analyzed

Analysis populations for this study were as follows:

- The FAS defined as the subset of randomized participants who received at least 1 dose of the study vaccine in the primary series.
- The FASI is defined as a subset of the FAS, including all participants from FAS who have a baseline RVNA titer lower than 0.5 IU/mL.
- Two PPASs are defined for key immunogenicity objectives: PPAS for D42 and PPAS for D28. These analysis sets were used for analysis of primary (PPAS D42) and secondary (PPAS D28) NI objective evaluation at D28 for participants in Primary Series Cohort 1 and Cohort 2.
- The SafAS in primary series was defined for each dose as the subset of participants having received this dose.

Reviewer Comment: For the analysis of the 5th secondary immunogenicity objective comparing 2-dose Imovax Rabies at D28 versus 3-dose Imovax Rabies at D42, the following analysis sets were used: 2-dose Imovax Rabies: PPAS for D28 (main analysis) 3-dose Imovax Rabies: PPAS for D42 (main analysis) FASI, FAS (Cohort 1).

6.2.10.1.1 Demographics

Participant demographics were assessed by age (12-23 months, 2-11 years, 12-17 years, 18-40 years, 41-64 years and ≥65 years), sex (female, male), race and ethnicity.

In Cohort 1, Group 3 (3-dose group) mean age of pediatric (ages 0 – 17) and adult participants (≥ 18 years old) was 8.9 and 36.2 respectively. In Cohort 2, Group 6 (2-dose group) mean age of adult participants was 37.3.

Fewer males than females were included overall. For all participants, racial origin was Asian, and ethnicity was Not Hispanic or Latino.

Reviewer Comment: Of the 100 pediatric participants in Cohort 1, Group 3 (3-dose group), only 2 were in the 12–23-month age group. Of the adults, only 2 participants in Cohort 1, Group 3 (3-dose group) and none in Cohort 2, Group 6 (2-dose group) were ≥65 years of age.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

In Group 3 (3-dose group), 41 (20.5%) of participants, and in Group 6 (2-dose group), 25 (18%) participants reported at least one past and current significant medical history.

Reviewer Comment: The most commonly reported conditions across Groups 3 and 6 were dyslipidemia, hypertension, and diabetes mellitus. The nature of the reported medical conditions was unlikely to affect the immunogenicity results.

Concomitant Medication Use

Overall, 23 (11.5%) participants in Group 3 (3-dose group) and 8 (5.8%) participants in Group 6 (2-dose group) reported at least 1 reportable concomitant medication in the Primary Series. Two (1.4%) participants in Group 6 reported concomitant medications considered by the Applicant as “Protocol-restricted medication” (rabies vaccine and Diphtheria Tetanus Toxoid vaccine).

Reviewer comment: The difference in percentage of participants that reported concomitant medication use in Groups 3 and 6 might be attributable to the overall small number of participants reporting concomitant medication use.

6.2.10.1.3 Participant Disposition

Table 18. Number of Planned and Actual Participants in Primary Series Cohort 1 Group 3 (3-dose) and Cohort 2 Group 6 (2-dose)

Participants	Group 3 (3-dose) Imovax Rabies	Group 6 (2-dose) Imovax Rabies
Adults	**--**	**--**
Planned	101	138
Randomized	100	139
SafAS	100	139
FAS	100	139
FASI	82	130
PPAS at D28	79	124
PPAS at D42	79	NA

Participants	Group 3 (3-dose) Imovax Rabies	Group 6 (2-dose) Imovax Rabies
Pediatric	--	--
Planned	101	-
Randomized	100	-
SafAS	100	-
FAS	100	-
FASI	91	-
PPAS at D28	81	-
PPAS at D42	83	-

Source: Adapted from 103931.5342, Clinical Study Report, Tables S1 and S2, pp. 32-34
Abbreviations: NA=Not applicable; SafAS=Safety analysis set; FAS=Full analysis set; FASI=Full analysis set for immunogenicity; PPAS=Per protocol analysis set

In Group 3 (3-dose), 196/200 participants completed active phase of primary series. Four adult participants discontinued the study after V05 because of protocol deviations (terminated early).

In Group 6 (2-dose), 138/139 participants completed the active phase of primary series. One participant discontinued the study after V03 AE: suspected exposure to rabies (terminated early).

Reviewer Comment: In Cohort 2, the Applicant initially planned to enroll 138 participants but ended up randomizing 139 participants due to the replacement of one participant, who was terminated early (after V03) for suspected rabies exposure.

See Section 9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered for additional information on study participants terminated early for potential rabies exposure.

6.2.11 Efficacy Analyses

For this sBLA, the 5th secondary immunogenicity objective with related endpoint is presented by the Applicant to support the claim that a 2-dose PrEP regimen of Imovax Rabies is NI to the 3-dose PrEP regimen.

6.2.11.1 Analyses of Primary Endpoint(s)

The primary endpoint was related to the VRVg-2 vaccine, hence it will not be discussed in this review beyond stating that the primary endpoint was met.

6.2.11.2 Analyses of Secondary Endpoints

The 5th secondary immunogenicity endpoint was defined as follows:

- NI of 2-dose Imovax Rabies at D28 versus 3-dose Imovax Rabies at D42 in overall participants in Imovax Rabies group in Cohort 1, Group 3 (3-dose group) only, based on NI margin of −10%.
- In addition, pre-planned supplemental analysis was performed based on NI margin of −5%.

In the PPAS, the NI of 2-dose Imovax Rabies (Group 3 at D28) versus 3-dose Imovax Rabies (Group 3 at D42) was demonstrated based on RVNA titer (≥0.5 IU/mL), both based on NI margin of -10% and -5%.

Table 19. Percentage of Participants Achieving a RVNA Titer ≥0.5 IU/mL – PPAS, Evaluating Noninferiority of Imovax Rabies at D28 (after 2-doses) Versus Imovax Rabies at D42 (after 3 doses) in Group 3 (3-dose group)

Group 3 Imovax Rabies at D28 n/M	Group 3 Imovax Rabies at D28 %SC (95% CI)	Group 3 Imovax Rabies at D42 n/M	Group 3 Imovax Rabies at D42 %SC (95% CI)	Group 3 at D28 - Group 3 at D42 % (95% CI)
158/160	98.8% (95.6; 99.8)	160/160	100% (97.7: 100)	-1.3 (−4.4; 1.3)

Source: Adapted from 103931.5342, Clinical Study Report, Table 16; p 144.
Abbreviations: RVNA=rabies virus neutralizing antibody; D=Day; PPAS=Per-Protocol Analysis Set; CI=confidence interval n=number of participants who achieved a RVNA titer ≥0.5 IU/mL; SC=Seroconversion.
M=number of participants with available data for the endpoint

The 6th secondary endpoint was descriptive and defined as follows: Immune response after 2-dose Imovax Rabies at D28 versus 3-dose Imovax Rabies at D42 (PPAS for D28 and PPAS for D42).

Table 20. Primary Series - Immunogenicity Criteria - RVNA Titers (RFFIT Method - IU/mL) - [D0 - D28 - D42] – PPAS

Event	Group 3 (3-dose group) Imovax Rabies (N=162)	Group 6 (2-dose group) Imovax Rabies (N=124)	Groups 3+6 Imovax Rabies (N=284)
Pre-dose 1	--	--	--
RVNA titer ≥0.2 IU/mL n (%) [95% CI]	0 [0, 2.3]	0 [0, 2.9]	0 [0, 1.3]
GMT [95% CI]	0.101 [0.100, 0.101]	0.100 [0.100, 0.101]	0.101 [0.100, 0.101]
Post-dose 2 (D28)	--	--	--
Available RVNA titer	160	124	284
RVNA titer ≥0.5 IU/mL n (%) [95% CI]	158 (98.8) [95.6, 99.8	119 (96.0) [90.8, 98.7]	277 (97.5) [95.0, 99.0]
GMT [95% CI]	5.13 [4.48, 5.87]	3.91 [3.25, 4.70]	4.56 [4.08, 5.09]
Post-dose 3 (D42)	--	--	--
Available RVNA titer	162	-	-
RVNA titer ≥0.5 IU/mL n (%) [95% CI]	162 (100) [97.7, 100]	-	-
GMT [95% CI]	16.4 [14.7, 18.3]	-	-

Source: Adapted from 103931.5342, Clinical Study Report, Tables 8.2.19 and 8.2.20 pp: 574-597
Abbreviations: GMT=Geometric mean titer; RVNA=rabies virus neutralizing antibody; D=Day; RFFIT=Rapid Fluorescent Focus Inhibition Test; PPAS=Per-Protocol Analysis Set; CI=confidence interval n=number of participants experiencing the endpoint listed; N=number of participants in per-protocol analysis set
Note: For Group 6, only 28-day RVNA titer is available.

Reviewer Comment: The 5th and 6th secondary immunogenicity objectives and related endpoint were the only Study VRV12 immunogenicity objectives relevant to this sBLA. The SAP states that the primary and the previous secondary immunogenicity objectives must have been met sequentially to proceed with analysis of every next secondary objective. The primary as well as the first 3 secondary objectives were met. The 4th

secondary objective (b) (4) *; however, this objective was related to VRVg and did not impact the 2-dose vs 3-dose Imovax Rabies evaluation.*

Even though the lower bound of the immunogenicity margin was defined by the Applicant as −10%, the Applicant conducted a pre-specified supplementary analysis with −5% margin, as requested by CBER. The NI endpoint was met with both −10% and −5% margin, hence providing evidence that 2-dose PrEP Imovax Rabies regimen is NI to the 3-dose one.

The 6th secondary objective was descriptive. It is notable that at D28 (after 2-doses of Imovax Rabies) 158/160 (98.8%) participants in Group 3, and 119/124 (96%) participants in Group 6 had RVNA titer ≥0.5 IU/mL. Also, two participants in Group 6 did not respond (e.g., RVNA titers were <0.2 IU/mL). Review of the available data from these two participants did not reveal medial history or concomitant medication use that could explain reason for lack of response to vaccination. One of the two participants was obese, that according to the Applicant, might have contributed to lack of vaccine response. The Applicant also noted that "previous studies have also shown that some subjects were low responders, slow responders, or non-responders to the rabies vaccines or other licensed vaccines without any underlying or immunosuppressive conditions, but the immunological mechanisms are unknown and are most likely host-related than vaccine-related." (Wiedermann 2016, Pineda-Peña 2024)

6.2.11.3 Subpopulation Analyses

The Applicant provided immunogenicity analyses by age class: 12-23 months, 2-11 years, 12-17 years, 18-40 years, 41-64 years and ≥65 years.

Immunogenicity evaluation of the PrEP regimen by age group

The immunogenicity evaluations of the PrEP regimens for Group 3 (3-dose regimen) are presented below on the FASI:

Table 21. RVNA Titers (RFFIT Method - IU/mL) - [D0, D28, D42], by Age Group – Group 3 (3-dose group) FASI

Event	Group 3 12-23 Months N=2 n (%) [95% CI]	Group 3 2-11 Years N=63 n (%) [95% CI]	Group 3 12-17 Years N=26 n (%) [95% CI]	Group 3 18-40 Years N=59 n (%) [95% CI]	Group 3 41-64 Years N=22 n (%) [95% CI]	Group 3 ≥65 Years N=1 n (%) [95% CI]
Pre-Dose 1 (D0)						
N	2	63	26	59	22	1
Titer ≥0.5 IU/mL	0 (0.0) [0, 84.2]	0 [0, 5.7]	0 [0, 13.2]	0 [0, 6.1]	0 [0, 15.4]	0 [0, 97.5]
GMT	0.100 [NC, NC]	0.102 [0.098, 0.105]	0.100 [NC, NC]	0.108 [0.100, 0.116]	0.100 [NC, NC]	0.100 [NC, NC]
D28 (Post-Dose 2)						
Available data	1	61	26	59	22	1
Titer ≤0.2 IU/mL n (%)	0 (0.0)	0 (0.0)	0	0	0	0
Titer ≥0.5 IU/m ≥65 years L	1 (100) [2.5, 100]	61 (100) [94.1, 100]	26 (100) [86.8, 100]	59 (100) [93.9, 100]	21 (95.5) [77.2, 99.9]	0 [0, 97.5]
GMT	10.5 [NC, NC]	7.87 [6.68, 9.26]	7.1 [5.5, 9.15]	4.33 [3.40, 5.50]	2.65 [1.89, 3.73]	0.300 [NC, NC]
D42 (Post-Dose 3)						
Available data	1	63	26	59	22	1
Titer ≤0.2 IU/mL n (%)	0	0	0	0	0	0
Titer ≥0.5 IU/mL	1 (100) [2.5, 100]	63 (100) [94.3, 100]	26 (100) [86.8, 100]	59 (100) [93.9, 100]	22 (100) [84.6, 100]	1 (100) [2.5, 100]
GMT	71.7 [NC, NC]	23.2 [19.7, 27.2]	18.1 [14.3, 23.1]	13.5 [11.7, 15.7]	11.0 [8.12, 14.9]	1.51 [NC, NC]

Source: Adapted from 103931.5342/0; VRV12 Published CSR-Appendix 15: Complimentary listings and analysis, Table 2.11 (pgs. 132-151)
Abbreviations: GMT=Geometric mean titer; N=number of participants in full analysis set for immunogenicity, by age group; n=percentage of participants fulfilling the item listed; NC=non-calculable; CI=confidence interval; RVNA=rabies virus neutralization assay; RFFIT= Rapid fluorescent focus inhibition test; FASI: Full analysis set for immunogenicity.
Group 3=3-dose regimen IM Imovax Rabies group (pediatric participants only)

The immunogenicity evaluations of the PrEP regimens for Group 6 (2-dose group) as well as adult age groups combined as Groups 3 + 6 is presented below on the FAS:

Table 22. RVNA Titers (RFFIT Method - IU/mL) - [D0 - D28 - D42], by Age Group –Group 6 (2-dose group) and Groups 3+6 (3-dose + 2-dose groups); FASI

Event	Group 6 18-40 N=130 n (%) [95% CI]	Group 6 41-64 N=130 n (%) [95% CI]	Group 6 ≥65 N=130 n (%) [95% CI]	Group 3+6 18-40 N=303 n (%) [95% CI]	Group 3+6 41-64 N=303 n (%) [95% CI]	Group 3+6 ≥65 N=303 n (%) [95% CI]
Pre-Dose 1 (D0)	--	--	--	--	--	--
Available Data	75	55	0	134	77	1
Titer ≥0.5 IU/mL	0 [0, 4.8]	0 [0, 6.5]	-	0 [0, 2.7]	0 [0, 4.7]	0 [0, 97.5]
GMT	0.105 [0.099, 0.112]	0.101 [0.099, 0.103]	-	0.106 [0.102, 0.111]	0.101 [0.099, 0.102]	0.100 [NC, NC]
D28 (Post-Dose 2)	--	--	--	--	--	--
Available data	74	55	-	133	77	1
Titer ≤0.2 IU/mL n (%)	1	1	-	1	1	0
Titer ≥0.5 IU/mL	71 (95.9) [88.6, 99.2]	53 (96.4) [87.5, 99.6]	-	130 (97.7) [93.5, 99.5]	74 (96.1) [89.0, 99.2]	0 [0, 97.5]
GMT	4.91 [3.78, 6.37]	3.27 [2.5, 4.28]	-	4.64 [3.88, 5.54]	3.08 [2.49, 3.81]	0.300 [NC, NC]

Source: Adapted from 103931.5342/0; VRV12 Published CSR-Appendix 15: Complimentary listings and analysis, Table 2.11 (pgs. 161-190)
Abbreviations: GMT=Geometric mean titer; N=number of participants in full analysis set for immunogenicity; n=percentage of participants fulfilling the item listed; NC=non-calculable; CI=confidence interval; RVNA=rabies virus neutralization assay; RFFIT= Rapid fluorescent focus inhibition test; FASI: Full analysis set for immunogenicity.
Group 3=3-dose regimen IM Imovax Rabies group
Group 6=2-dose regimen IM Imovax Rabies group

Reviewer Comment: As expected, all pediatric participants seroconverted and mounted higher RVNA titers compared with adult participants. RVNA titers decreased with increased age, though a majority of participants responded to vaccination (developed RNVA Titer at least ≥0.2 IU/mL) and seroconverted (defined as RNVA titer ≥0.5 IU/mL). Two adult participants in Group 6 did not develop immune response (i.e., RVNA titer remained below detection threshold).

6.2.11.4 Dropouts and/or Discontinuations

See section 6.2.10.1.3.

6.2.11.5 Exploratory and Post Hoc Analyses

The following exploratory analyses were conducted that are relevant to this sBLA: Percentage of participants in Cohort 1 achieving an RVNA titer ≥0.5 IU/mL of Imovax Rabies at D28 versus Imovax Rabies at D42 by age group in the PPAS, in the FASI, and in the FAS.

- In the pediatric population (<18 years), the difference in the percentage of participants achieving an RVNA titer ≥0.5 IU/mL after 2 doses (Group 3 at D28) and 3 doses of Imovax Rabies (Group 3 at D42) was 0% (95% CI: −4.5%, 4.5%) in the PPAS.

- In the adult population (≥18 years), the difference in the percentage of participants achieving an RVNA titer ≥0.5 IU/mL after 2 doses (Group 3 at D28) and 3 doses of Imovax Rabies (Group 3 at D42) were −2.5% (95% CI: −8.8%, 2.5%) in the PPAS.

Reviewer comment: In the adult population, the difference in percentage of participants achieving an RVNA titer ≥0.5 IU/mL after the 2-doses and 3-doses was -2.5%, with a wide confidence interval (-8.8%; 2.5%). Since this analysis was exploratory in nature, formal hypothesis testing was not performed. Wide conference interval may be attributed to smaller sample size within individual age group.

6.2.12 Safety Analyses

6.2.12.1 Methods

As the primary comparison for safety and effectiveness is between Groups 3 and 6, which differed only in the number of administrations of the same vaccine (Imovax Rabies) by the same route (IM), the safety review focused mainly on evaluation of any unusual AEs not previously described in the product package insert.

The analysis set used for safety was the SafAS defined as a subset of randomized participants who received at least 1 dose of the study vaccines. Safety for study participants was also assessed, based on the study-defined age categories: 12 through 23 months, 2 through 11 years, 12 through 17 years, 18 through 40 years, 41 through 64 years, and ≥65 years.

All randomized participants in Groups 3 and 6 received the study vaccine. The Active Phase of the Primary Series was completed by 196/200 (98.0%) participants in Group 3 (3-dose group) and 138/139 (99.3%) participants in Group 6 (2-dose group). The 6-month follow-up (Cohort 1) was completed by 200 (100%) participants in Group 3 (3-dose group).

6.2.12.2 Overview of Adverse Events

Table 23. VRV12 - Primary Series - Solicited Injection Site and Systemic Reactions Within 7 Days- SafAS

Participants Experiencing at Least One	Group 6: 2-dose group (Adults) Imovax Rabies 2-Dose (N=139) n/M % (95% CI)	Group 3: 3-dose group (Overall) Imovax Rabies 3-Dose (N=200) n/M % (95% CI)	Group 3: 3-dose group (Adults) Imovax Rabies 3-Dose (N=100) n/M % (95% CI)	Group 3: 3-dose group (Pediatrics) Imovax Rabies 3-Dose (N=100) n/M % (95% CI)
Solicited injection site reaction	43/139 30.9 (23.4; 39.3)	107/200 53.5 (46.3; 60.6)	52/100 52.0 (41.8; 62.1)	55/100 55.0 (44.7; 65.0)
Grade 3 injection site reaction	0/139 0 (0; 2.6)	0/200 0 (0; 1.8)	0/100 0 (0; 3.6)	0/100 0 (0; 3.6)
Injection site tenderness/pain	43/139 30.9 (23.4; 39.3)	106/200 53.0 (45.8; 60.1)	52/100 52.0 (41.8; 62.1)	54/100 54.0 (43.7; 64.0)

Participants Experiencing at Least One	Group 6: 2-dose group (Adults) Imovax Rabies 2-Dose (N=139) n/M % (95% CI)	Group 3: 3-dose group (Overall) Imovax Rabies 3-Dose (N=200) n/M % (95% CI)	Group 3: 3-dose group (Adults) Imovax Rabies 3-Dose (N=100) n/M % (95% CI)	Group 3: 3-dose group (Pediatrics) Imovax Rabies 3-Dose (N=100) n/M % (95% CI)
Injection site erythema	1/139 0.7 (0; 3.9)	6/200 3.0 (1.1; 6.4)	0/100 0 (0; 3.6)	6/100 6.0 (2.2; 12.6)
Injection site swelling	1/139 0.7 (0; 3.9)	13/200 6.5 (3.5; 10.9)	4/100 4.0 (1.1; 9.9)	9/100 9.0 (4.2; 16.4)
Solicited systemic reaction	33/139 23.7 (16.9; 31.7)	93/200 46.5 (39.4; 53.7)	48/100 48.0 (37.9; 58.2)	45/100 45.0 (35.0; 55.3)
Grade 3 systemic reaction	0/139 0 (0; 2.6)	1/200 0.5 (0; 2.8)	0/100 0 (0; 3.6)	1/100 1.0 (0; 5.4)
Fever	0/139 0 (0; 2.6)	4/200 2.0 (0.5; 5.0)	1/100 1.0 (0; 5.4)	3/100 3.0 (0.6; 8.5)
Vomiting	-	1/2 50.0 (1.3; 98.7)	-	1/2 50.0 (1.3; 98.7)
Crying abnormal	-	1/2 50.0 (1.3; 98.7)	-	1/2 50.0 (1.3; 98.7)
Drowsiness	-	0/2 0 (0; 84.2)	-	0/2 0 (0; 84.2)
Appetite loss	-	0/2 0 (0; 84.2)	-	0/2 0 (0; 84.2)
Irritability	-	0/2 0 (0; 84.2)	-	0/2 0 (0; 84.2)
Headache	8/139 5.8 (2.5; 11.0)	46/198 23.2 (17.5; 29.7)	22/100 22.0 (14.3; 31.4)	24/98 24.5 (16.4; 34.2)
Malaise	12/139 8.6 (4.5; 14.6)	48/198 24.2 (18.4; 30.8)	25/100 25.0 (16.9; 34.7)	23/98 23.5 (15.5; 33.1)
Myalgia	29/139 20.9 (14.4; 28.6)	78/198 39.4 (32.5; 46.6)	41/100 41.0 (31.3; 51.3)	37/98 37.8 (28.2; 48.1)

Source: Adapted from 103931.5342, Summary of Clinical Safety, Tables 11 and 12 pp: 42 and 44-45.
Abbreviations: N=number of participants experiencing the endpoint listed; M=number of participants with available data for the relevant endpoint
Solicited systemic reactions were collected by different age group: fever, vomiting, crying abnormal, drowsiness, appetite loss, and irritability were collected for participants 15 to 23 months; fever, headache, malaise, and myalgia were collected for participants ≥2 years

Reviewer Comment: Participants who received 2-dose Imovax versus 3-dose Imovax PrEP reported fewer local and systemic reactogenicity events. One pediatric participant (12-year-old female) reported 2 Grade 3 solicited systemic reactions (1 malaise [0.5%] and 1 myalgia [0.5%]) after the first injection. Both reactions resolved within 2 days. Imovax Rabies vaccine has a well characterized safety profile. Results shown above do not reveal unexpected findings.

6.2.12.3 Deaths

No deaths were reported.

6.2.12.4 Nonfatal Serious Adverse Events

A total of 5 (2.5%) participants in Group 3 (3-dose group) reported an SAE: 1 (0.5%) participant during the active phase of the primary series and 4 participants (2.0%) during the 6-month follow-up period. None of these SAEs were assessed as related to the study vaccine by the investigator. No SAEs were reported in Group 6 (2-dose group).

- A 52-year-old female with no medical history who developed knee ligament injury 169 days after the third dose injection, when she fell out of a car. The SAE did not cause discontinuation of the participant from the study.
- A 16-year-old female with no medical history who had a sealed ruptured cornea at left eye 73 days after the third dose injection. The participant's left eye was "accidently pierced by a needle." Her eye injury was subsequently complicated by an eye infection and required treatment at the hospital. The SAE did not cause discontinuation of the participant from the study.
- A 19-month-old male with no medical history who developed productive cough and vomiting 5 days after the third dose injection. Participant was treated by a health care provider for acute bronchitis. He also had solicited events of abnormal crying and vomiting (both Grade 1) which resolved the next day. Because cough did not resolve with initial treatment, participant was taken to the hospital by his mother. He was subsequently required admission to hospital and treatment for his bronchitis. During hospitalization, the participant received oral carbocisteine and salbutamol/normal saline solution via nebulizer. The participant was discharged from the hospital 3 days after admission, and the next day after discharge, the event of acute bronchitis was reported as resolved. Three days after the bronchitis was reported resolved, the participant had an unsolicited event of otitis media (Grade 1), followed by acute respiratory infection two days afterwards (Grade 1). The events subsequently resolved. The SAE of acute bronchitis did not cause discontinuation of the participant from the study.
- A 13-year-old male with no medical history had an intentional paracetamol overdose. He received his last vaccine on February 23, 2025. The participant attempted suicide with approximately 50 tablets of paracetamol and was taken to the emergency department by his parents, 177 days after the third dose injection with control vaccine. He required admission to the hospital and treatment with unspecified drugs. He was discharged from the hospital with an unspecified antidepressant drug and follow up with the psychiatrist. Despite multiple follow-up attempts by the study site, the participant's parent did not respond. The Applicant states that the SAE did not cause discontinuation of the participant from the study.
- A 30-year-old female who received the 3rd dose of Imovax Rabies on February 4, 2020, became pregnant, and her date of LMP was 15 February 2020, i.e., 11 days after third dose injection. The participant had "inevitable abortion" (Grade 3, on 06 March 2020), 31 days after third dose injection. She had vaginal bleeding for five days. The participant underwent "conceptual removal" without hospitalization. She had no clear amniotic fluid or normal placenta. On 11 March 2020, the event of inevitable abortion resolved as the participant had spontaneous abortion. The SAE did not cause discontinuation of the participant from the study.

Reviewer Comment: The Applicant's assessment of the SAEs as not related to the study vaccine appears reasonable, based on the nature or timing of the events following vaccination.

6.2.12.5 Adverse Events of Special Interest (AESIs)

No AESIs were reported.

6.2.12.6 Clinical Test Results

The evolution of biological laboratory parameters was not assessed in Study VRV12.

6.2.12.7 Dropouts and/or Discontinuations

Please see section 6.2.10.1.3.

6.2.13 Study Summary and Conclusions

Study VRV12 was a Phase 3, observer-blind, randomized, controlled multi-center study conducted in Thailand designed to evaluate the immunogenicity and safety of the Applicant's investigational vaccine, VRVg-2, compared with licensed Verorab (ex-US licensed) and Imovax Rabies (US licensed). The study was initially designed to compare 3-dose PrEP regimens. However, following ACIP's updated recommendations for a 2-dose instead of a 3-dose PrEP regimen, the Applicant, with concurrence from CBER, modified the ongoing study to add a second cohort of participants and several secondary and exploratory objectives, including to evaluate a D0, D7 2-dose Imovax Rabies PrEP regimen as compared with a 3-dose regimen.

Immunogenicity

At D28 (21 days after the 2nd dose and prior to the 3rd dose), 98.8% of participants in the 3-dose group had an RVNA titer ≥0.5 IU/mL. At D42 (14 days after the 3rd dose), 100% of participants in the 3-dose group had an RVNA titer ≥0.5 IU/mL. The difference in the percentage of participants who achieved the 0.5 IU/mL threshold was −1.3% (95% CI: −4.4; 1.3), greater than the pre-specified NI margins of −10% (Applicant success criterion used to power the study) and −5% (CBER requested success criterion); thereby, meeting the immunogenicity NI endpoint.

Safety

The safety profile of Imovax Rabies is well characterized from decades of clinical experience. In Study VRV 12, site tenderness/pain was the solicited injection site reaction most frequently reported across age groups (pediatrics 54% and adults 52%) and regimens (30.9% 2-dose and 53% 3-dose). Myalgia was the most frequently reported solicited systemic reaction (20.9% 2-dose and 39.4% 3-dose). Most of the reactions were mild to moderate in intensity and resolved within 3 days.

Overall, Imovax Rabies administered as a 2-dose IM PrEP regimen was well tolerated with local and systemic reactogenicity reported at percentages lower than that of the standard 3-dose IM PrEP regimen. No new safety concerns were identified.

7. INTEGRATED OVERVIEW OF EFFICACY

While both studies, VAJ00001 and VRV12, evaluated 2- and 3-dose Imovax Rabies PrEP regimens, an ISE was not performed, because these studies were designed to assess immunogenicity at different time points.

Please refer to Sections 6.1 and 6.2 for discussion of the individual studies.

8. INTEGRATED OVERVIEW OF SAFETY

While both studies, VAJ00001 and VRV12, evaluated 2- and 3-dose Imovax Rabies PrEP regimens, an ISS was not performed due to different study designs, safety monitoring, data collection and data reporting periods.

Please refer to Sections 6.1 and 6.2 for discussion of the individual studies.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

Both studies VAJ00001 and VRV12 evaluated pediatric and geriatric participants, though the number of enrolled geriatric participants (65 years and older) was limited to 2 participants. Please see individual studies Section 6.1 and 6.2 for details. Pregnant women were excluded from participation in this study; however, limited data are available based on 10 reported pregnancies. Immunosuppressed individuals were excluded from study participation.

9.1.1 Human Reproduction and Pregnancy Data

Overall, available information regarding the use of Imovax Rabies vaccine in pregnant, lactating women and females and males of reproductive potential is limited. Adequate and well-controlled studies have not been conducted on Imovax Rabies vaccine administration in pregnant or lactating women in the U.S. and globally.

Data from Study VAJ0001: No exposures to the study products during pregnancy were reported. Nine participants in the Imovax Rabies IM groups reported “unexposed” pregnancies during the study; six in 2-dose group, three in 3-dose group, including the two SAEs related to pregnancy: stillborn in one participant and spontaneous abortion at 15 weeks gestation in another. Both SAEs occurred in Group 2, discussed in section 6.1.12.4 of the review). All 6 pregnancies in Group 1 resulted in normal live births with no congenital anomalies reported; the shortest interval between LMPs and the second (last) vaccination was 127 days. One normal pregnancy in Group 2 resulted in twin neonates without abnormalities delivered by Caesarian section; the mother’s LMP was 222 days after her third Imovax Rabies vaccination. All four pregnancies in Group 3 (Imovax Rabies, ID administration) resulted in live births of neonates without congenital anomalies; the shortest interval between the LMP and last dose of Imovax Rabies was 31 days.

Data from Study VRV12: One pregnancy was reported in 3-dose group in a participant who received the 3rd Imovax Rabies vaccine dose 11 days prior to her LMP. The participant had “inevitable abortion” 31 days after the third dose injection with Imovax Rabies. The pregnancy ended 5 days later with a spontaneous abortion (at <20 weeks of gestation).

PrEP may be considered during pregnancy if substantial risk of exposure to rabies exists. Due to the potential consequences of inadequately managed rabies exposure, pregnancy is not a contraindication to PEP.

9.1.2 Use During Lactation

No data are available on whether Imovax Rabies is excreted in human milk or assessing the effects of Imovax Rabies on breastfed infants or on milk production or excretion. The developmental and health benefits of breastfeeding, any potential adverse effects of vaccination, and the need for Imovax Rabies should be evaluated when considering whether to vaccinate a lactating mother.

9.1.3 Pediatric Use and PREA Considerations

Imovax Rabies is indicated for use in all ages. The Applicant is seeking to add a 2-dose PrEP regimen in the pediatric population. This supplement introduces a new dosing regimen which triggers PREA.

In the pre-sBLA WRO communication the CBER issued in May 2024, CBER advised the Applicant to include a PSP in the sBLA submission and to provide justification for extrapolation in infants < 2 years old in the Pediatric Study Plan (PSP).

Extrapolation of safety and effectiveness data from children and adolescents 2 years to <18 years of age who were immunized with Imovax Rabies vaccine to neonates and infants <2 years of age was supported by the following reasons: (1) the pathogenesis and disease caused by rabies virus is the same regardless of age, and (2) In both VAJ00001 and VRV12, 100% of participants 2 to <18 years of age had a RVNA titer ≥ 0.5 IU/mL by day 21 after the last vaccination. Overall, no noteworthy differences were reported across Imovax Rabies study groups in the safety profiles among participants 2 to <12 years of age, 12 to <18 years of age, and adults. Accordingly, the safety and immunogenicity of Imovax Rabies vaccine in neonates and infants <2 years of age are also expected to be similar to the safety and immune responses following Imovax Rabies vaccination in older children 2 years to <18 years of age.

Of note, one participant in Study VRV12 in 12–23-month age group with evaluable immunogenicity result on D28 (21 days after the 2nd Imovax Rabies vaccine dose) developed RVNA titer ≥0.5 IU/mL (GMT 10.5), suggestive of strong immune response.

9.1.4 Immunocompromised Patients

It is generally accepted that immune responses to vaccines, including rabies vaccines, may be sub-optimal in participants with primary or secondary immunodeficiencies. Participants with primary or secondary immunodeficiencies were excluded from Studies VAJ00001 and VRV12.

Data on response to rabies vaccine is limited to small studies and case reports. Overall, the available literature suggests that patients with suppressed immune status might develop lower or inconsistent antibody response following PrEP and PEP vaccination with rabies vaccine compared to healthy population (Thisyakorn 2000, Cramer 2008). CDC has special considerations in the approach to PrEP in immunocompromised population, where they recommend delaying PrEP until a temporary immunocompromising condition has resolved or immunosuppressive medications can be withheld. If an immunocompromising condition cannot be temporarily reversed, rabies vaccines can be administered, but antibody titer should be checked no sooner than 1

week (preferably 2–4 weeks) after completion of the 2-dose PrEP series and all booster doses.

Reviewer comment: When PrEP is necessary for an immunocompromised person and cannot be delayed until the immunosuppressing condition resolves or immunosuppressive medications are discontinued, PrEP may be administered with the understanding that the patient may not respond adequately. Available data do not clearly indicate whether a 2-dose or 3-dose PrEP regimen is preferred in this population, as some patients may fail to mount an adequate immune response even after 3 doses and may require additional booster doses. Healthcare practitioners administering rabies PrEP must be familiar with and follow current CDC and ACIP guidelines when making PrEP decisions for immunocompromised patients.

9.1.5 Geriatric Use

No geriatric patients were enrolled in Study VAJ00001. Data are available from only 1 participant ≥ 65 years of age in Study VRV12, who developed an RVNA titer 0.3 IU/mL after 2-dose PrEP but did not seroconvert (i.e., RVNA titer did not reach ≥0.5 IU/mL). However, this participant seroconverted after 3-doses of Imovax Rabies PrEP (RVNA titer was 1.51 IU/mL).

Reviewer comment: Based on data from a single participant it is difficult to draw conclusions on the adequacy of 2-dose PrEP or make a strong recommendation for requiring 3-dose PrEP in individuals ≥ 65 years of age.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

We queried the Applicant for information regarding participants who could have been exposed to rabies after getting any number of doses of Imovax Rabies for PrEP (IR #2). The Applicant reported that they conducted a comprehensive crosscheck across the different clinical database domains for Studies VAJ00001 and VRV12 and the global pharmacovigilance database. Nineteen such cases were identified, out of which eighteen were reported in Study VAJ00001, and one in Study VRV12. Time interval from suspected rabies exposure to PEP initiation were either reported within days, or information was not available. Time interval from suspected rabies exposure to last known safety follow-up varied substantially, 6 days being the shortest and 334 the longest. In 3 cases the time interval from suspected rabies exposure to last known safety follow-up was marked as unavailable. All participants at study end were reported as alive. Data on confirmation of rabies exposure were not available.

Reviewer comment: In this reviewer's opinion, limited information is available to make conclusions regarding rabies exposures and outcomes; however, available data did not raise safety concerns.

10. CONCLUSIONS

The Applicant submitted clinical data from two clinical studies, VAJ00001 and VRV12. CBER had previously reviewed data from non-IND Study VAJ00001 and determined that because it narrowly missed its primary NI endpoint, it could not be uses as the primary data to support labeling of a 2-dose PrEP regimen. The Applicant subsequently proposed and CBER concurred with adding additional dosing groups and appropriately

timed immunogenicity and safety assessments to the already ongoing VRV12 study. Study VRV12 met its objective, providing evidence that 2-dose IM PrEP is NI to the already licensed 3-dose series.

10.1 Risk-Benefit Considerations

Table 24 below summarizes a qualitative risk-benefit assessment for use of 2-dose Imovax Rabies vaccine for the PrEP indication against rabies based upon the individual judgment of the clinical reviewer.

Table 24. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Human rabies is an acute, progressive encephalomyelitis that is nearly always fatal once symptoms begin. • PEP includes rabies vaccination and immunoglobulin, is highly effective if administered after an exposure occurs, and is widely available in the U.S. • A small subset of persons has a higher level of risk for being exposed to rabies virus than does the general U.S. population; these persons are recommended to receive PrEP. • PrEP does not obviate the need for PEP; however, it does simplify the rabies PEP schedule, as well as eliminate the need for immunoglobulin administration (Rao 2022).	• Rabies is an acute, progressive, fatal disease. • PEP is effective in preventing rabies disease. • High-risk persons are recommended to receive PrEP. • PrEP simplifies but does not eliminate the need for PEP.
Unmet Medical Need	• Imovax Rabies is one of two vaccines approved in the U.S. for prevention of rabies. • As PEP, rabies vaccine is used in conjunction with rabies immunoglobulin in rabies immune-naïve persons. • Aside from rabies vaccines, no other drug or biologic is approved for prevention of rabies infection as a stand-alone measure. • In the U.S., ACIP recommends PrEP with 2 doses of rabies vaccine for most individuals at risk for rabies exposure. ACIP states that "robust data indicates people are adequately protected for rabies exposures through the 3-year time point after completion of a 2-dose primary series, and do not need to receive the 3rd dose before traveling or beginning a job that requires rabies PrEP.." "More people who are at-risk and recommended by ACIP to receive PrEP will be vaccinated because of the fewer doses and resulting lower costs." • The current Imovax Rabies USPI only specifies a 3-dose PrEP regimen, diverging from U.S. clinical practice, which follows the ACIP recommendation. • It is anticipated that 2-dose PrEP regimens will be used more routinely in the U.S. by health care providers as shortened regimen can reduce cost and increase compliance. • It is critical that the 2-dose PrEP regimen provides adequate immune priming, thus allowing for rapid reappearance of a protective level of RVNA after a post-exposure dose, as no RIG is to be given on subsequent exposure to those who had previously received a PrEP regimen.	• PrEP simplifies but does not eliminate the need for PEP. By eliminating the need for concurrent administration of RIG, PrEP may provide an advantage when sourcing RIG is difficult or by reducing exposure to potential risks associated with RIG administration.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Clinical Benefit	• Data from two clinical trials in adult and pediatric participants were submitted, in support of including the 2-dose PrEP regimen in the USPI as one of the specified regimens.for Imovax Rabies. • Study 1 did not meet its primary immunogenicity objective, which was to show that 2-dose Imovax Rabies regimen was NI to 3-dose regimen. In this study, all participants developed adequate vaccine response after sPEP, consistent with a desired anamnestic response. • Study 2 pre-specified a longer time interval from first vaccine-dose administration to assessment of the vaccine response. The primary objective of NI of the 2-dose regimen to the 3-dose regimen was met. This study was designed for another primary endpoint, but a secondary endpoint was added with an appropriately defined success criterion to support an NI assessment of the 2 doses of Imovax Rabies to 3 doses. • A PrEP regimen with fewer injections required over a shorter time interval could increase compliance with the vaccination regimen, although the Applicant did not submit data evaluating compliance.	• Potential for better adherence with recommendations for 2-dose vs 3-dose PrEP may translate into clinical benefit for those at continued risk of rabies exposure. • The evidence from sPEP suggests robust boosting of immune response with use of 2-dose PrEP regimen. • Although Study 1 failed (narrowly missed) its primary NI endpoint, the study was not done under IND and assessed immunogenicity at a suboptimal timepoint after the first vaccination. Study 2 had a more appropriately timed blood draw for the immunogenicity assessments and supported a 2-dose Imovax Rabies regimen as an acceptable rabies PrEP.
Risk	• Imovax Rabies has a well-established safety profile. The most common risks of Imovax Rabies administration are associated with the inflammation produced at the injection site and systemic reactions. In both Study 1 and Study 2, trends were similar between adult and pediatric participants. The most frequently reported solicited injection site reaction in both studies was injection site pain. The most frequent systemic reaction in Study 1 was headache and in Study 2 myalgia. Most solicited reactions were mild in intensity and resolved within 3 days.	• The data submitted indicate that the risk of vaccination with Imovax Rabies is minor.
Risk Management	• The most common risk of Imovax Rabies administration is reactogenicity events: injection site pain, headache; the risk is similar in both adult and pediatric groups. • No other safety signals were apparent in the clinical trial data submitted to the sBLA.	• Updated language in the PI and the current pharmacovigilance plan are expected to be adequate to manage any vaccine-associated risks.

10.2 Risk-Benefit Summary and Assessment

The safety profile from Studies VAJ00001 and VRV12 is favorable and Study VRV12 showed that when endpoints are appropriately defined (e.g., timing of blood draw for RVNA titers), 2-dose PrEP regimen is NI to 3-dose regimen. 2-dose PrEP regimen could offer the advantage of ease of implementation and the fact that the PrEP can be finished within 1 week (instead of previously required 3-4 weeks), could possibly increase compliance, especially in travelers who might have limited time to complete the vaccination series.

10.3 Discussion of Regulatory Options

The Applicant has requested and the data support extension of traditional approval of a 2-dose Imovax Rabies regimen for rabies PrEP in all age groups. The Applicant requested addition of a 2-dose regimen to the USPI and did not request removal or replacement of the 3-dose regimen already included in the USPI. We concur with that approach, acknowledging the potential need for individualizing selecting PrEP regimen in certain populations.

10.4 Recommendations on Regulatory Actions

In the opinion of this clinical reviewer, the safety and immunogenicity data provided support the addition to the USPI of the 2-dose Imovax Rabies regimen to be administered on Days 0 and 7 via the IM route for PrEP of rabies in all age groups.

10.5 Labeling Review and Recommendations

The Applicant's proposed revised USPI included safety and immunogenicity data from Studies VAJ00001 and VRV12. Study VAJ00001 was not conducted under IND, and FDA had not provided advice on timepoints of assessment of the immune response, which may have contributed to the study meeting its objective. Data generated from Study VRV12 is considered to be the more robust representation of immunogenicity of the proposed 2-dose Imovax Rabies regimen, as data generated from this study assessed the vaccine response at more appropriate timepoints.

Labeling negotiations requested that the Applicant:

- Revised PI to be Physician Labeling Rule (PLR) compliant.
- List the 3-dose Imovax Rabies PrEP regimen first, followed by the 2-dose regimen in Section 2.1
- Remove reactogenicity-related information of Study 2 from Section 6.1, Table 2 and include only Study 1 as the representative study. Add reactogenicity data for pediatric participants from Study 1. Present data for any grade as well as Grade 3 or higher reactogenicity events.
- Added Section 8.5 "Geriatric use" under Section 8 "USE IN SPECIFIC POPULATIONS".
- Revise Section 14 "CLINICAL STUDIES", section 14.1 Pre-Exposure Prophylaxis to include relevant information about study outcomes.

10.6 Recommendations on Postmarketing Actions

Routine pharmacovigilance.