Application Type	BLA Supplement
STN	103931/5342
CBER Received Date	09/23/2024
PDUFA Goal Date	07/24/2025
Committee Chair	Laura Montague
Clinical Reviewer(s)	Nana Aburjania
Project Manager(s)	Donna Elhindi; Jeffy Mattathil
Priority Review	No
Reviewer Name(s)	Peiran Liu Mathematical Statistician, VEB/DB/OBPV
Review Completion Date/Stamped Date	
Concurrence	Ye Yang Lead Mathematical Statistician, VEB/DB/OBPV
Supervisory Concurrence	Tsai-Lien Lin Branch Chief, VEB/DB/OBPV
Applicant	Sanofi Pasteur SA
Established Name	Rabies Vaccine
(Proposed) Trade Name	IMOVAX® Rabies
Dosage Form(s) and Route(s) of Administration	Freeze-dried suspension of inactivated rabies virus reconstituted with 1 mL solvent / Intramuscular injection into the deltoid muscle (or anterolateral thigh for toddlers)
Dosing Regimen	Two-dose pre-exposure prophylaxis at Day 0 and Day 7
Indication(s) and Intended Population(s)	Pre-exposure prophylaxis against rabies, in all age groups

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1. Executive Summary

The applicant, Sanofi Pasteur, submitted a Biologics License Application (BLA) Supplement (STN 103931/5342) to update the package insert to include an alternative 2-dose pre-exposure prophylaxis (PrEP) immunization schedule (at Day [D]0 and D7) for the primary vaccination against rabies in all age groups, in addition to the currently approved 3-dose PrEP schedule (at D0, D7, and D21 or D28) for intramuscular (IM) administration of Imovax Rabies, in line with the United States (U.S.) Advisory Committee on Immunization Practices (ACIP) recommendations in 2022.

The proposed alternative PrEP immunization schedule is supported by immunogenicity and safety data from two Phase 3 studies: VAJ00001 and VRV12. Of note, the immunogenicity and safety results from Study VAJ00001 were previously submitted under STN 103931/5296 and reviewed by Dr. Woobeen Lim. The submission was later voluntarily withdrawn by the applicant, as the study did not meet the primary non-inferiority objective for the 2-dose regimen as compared to the 3-dose regimen in terms of seroconversion rate, which was defined as achieving a rabies virus neutralizing antibody (RVNA) titer of ≥ 0.5 IU/mL at two weeks after the last vaccination. Under this application, data from Study VAJ00001 were resubmitted for descriptive purposes only. Accordingly, this review focuses on the interim clinical study report for Study VRV12, which included the key hypothesis-driven non-inferiority assessment comparing the two regimens of Imovax Rabies.

Study VRV12 is a Phase 3, multicenter, observer-blind, randomized controlled trial, conducted in healthy subjects aged 1 year and older in Thailand. A total of 1700 subjects were planned for enrollment across two cohorts. Cohort 1 included 505 pediatric and 505 adult subjects randomized 3:1:1 to receive VRVg-2 (investigational formulation of Purified Vero Rabies Vaccine – Serum Free [VRVg]), Verorab (not registered in the U.S.), or Imovax Rabies within each age group. All participants in Cohort 1 were scheduled to receive 3 primary series doses on D0, D7, and D28. Cohort 2 consisted of 690 adult subjects who were randomized to receive 2 primary series doses on D0 and D7, using the same 3:1:1 allocation ratio across the three products. Of note, the term "primary series" is used to distinguish from the booster phase of the trial. However, the booster phase is not considered in this review, as only VRVg-2 was administered during the booster phase to a subset of adult subjects from the two cohorts.

The primary objective of the study was to demonstrate the non-inferiority of VRVg-2 compared to Verorab and Imovax Rabies, in both pediatric and adult subjects from Cohort 1, based on differences in seroconversion rates measured 14 days after the third dose. Upon meeting the success criteria for the primary objective, five secondary objectives were to be tested sequentially. The first four secondary objectives were related to the primary investigational product, VRVg-2, while the fifth secondary objective addressed the key hypothesis of non-inferiority between the 2-dose and 3-dose PrEP schedules of Imovax Rabies. Specifically, the fifth secondary objective of the study was to demonstrate the non-inferiority of a 2-dose PrEP schedule compared to a 3-dose schedule of Imovax Rabies based on the difference in seroconversion rates (2-dose minus

3-dose), using a non-inferiority margin of -10%. In addition, a supplementary analysis assessed the same hypothesis via a -5% margin. Immune response was assessed at D28 (21 days after the second dose) for the 2-dose regimen, and at D42 (14 days after the third dose) for the 3-dose regimen. This comparison was conducted using pooled data from pediatric and adult subjects in Cohort 1 who received 3 PrEP doses of Imovax Rabies in the primary series.

The observed difference in seroconversion rates was -1.3% with a corresponding two-sided 95% confidence interval (CI) of (-4.4%, 1.3%). This estimate was based on 81 pediatric and 79 adult subjects who received 3 PrEP doses of Imovax Rabies and had immunogenicity data available at both D28 and D42. Since the lower bound of the CI was higher than the -5% non-inferiority margin, the non-inferiority of the 2-dose Imovax Rabies regimen compared to the 3-dose regimen in terms of seroconversion rate was successfully demonstrated. Of note, the fifth secondary objective, the key objective for this Supplemental BLA application, was tested in a scenario where the fourth secondary objective, assessing the seroconversion rate of the 2-dose VRVg-2, (b) (4) . Because the fourth secondary immunogenicity objective for VRVg-2 was not directly relevant to the current sBLA submission, the review team agreed to allow the applicant to proceed with submission of this supplement via a written response only (WRO) to the Type C meeting request under STN 103931/5333.

Pediatric and adult participants in Cohort 1 who received the 3-dose Imovax Rabies PrEP regimen and adult participants in Cohort 2 who received the 2-dose regimen were analyzed separately to assess the safety profiles of the two schedules. Solicited reactions within 7 days following any Imovax Rabies vaccine administration were reported more frequently in the 3-dose regimen than in the 2-dose regimen. Specifically, the rates of solicited reactions after any injection were 68.0% in pediatric subjects and 58.0% in adult subjects in Cohort 1, compared to 33.8% in adult subjects in Cohort 2. Most solicited reactions were mild to moderate in severity, with one pediatric subject experiencing malaise and myalgia post first injection classified as severe. Additionally, unsolicited adverse events (AEs) and serious adverse events (SAEs) were recorded throughout the study, but none were assessed as related to Imovax Rabies vaccination by the investigator.

In conclusion, no major statistical issues were identified in the immunogenicity and safety analyses. The data support inclusion of the 2-dose PrEP immunization schedule for Imovax Rabies.

2. Clinical and Regulatory Background

The immunogenicity and safety results of Study VAJ00001 were previously submitted under STN 103931/5296 on April 20, 2022, in support of the proposed 2-dose PrEP immunization schedule. However, the study did not meet its primary objective in demonstrating non-inferiority of the 2-dose regimen compared to the 3-dose regimen based on the difference in seroconversion rates using a non-inferiority margin of -5%. For additional statistical details, please refer to Dr. Woobeen Lim's review memo.

In response to regulatory feedback on December 9, 2022, the applicant voluntarily withdrew the efficacy supplement on January 5, 2023. Subsequently, Study VRV12, originally designed to evaluate the investigational product VRVg-2, was amended to include a non-inferiority assessment of the 2-dose PrEP regimen relative to the 3-dose PrEP regimen for Imovax Rabies (one of the control comparators) as the fifth secondary immunogenicity objective. In contrast to Study VAJ00001, which assessed immunogenicity 14 days after the second dose, Study VRV12 evaluated the immune response at 21 days after the second dose for the 2-dose Imovax Rabies regimen, to address the applicant's concerns regarding inadequacy of the timepoint for assessing seroconversion rate after the second dose.

Prior to this submission, the applicant requested a Type C meeting under STN 103931/5333. In the WRO to the meeting request, CBER acknowledged that interim data generated from Study VRV12 appeared to positively supplement the results of Study VAJ00001 in support of the 2-dose PrEP immunization schedule for Imovax Rabies.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practice and Data Integrity

No data integrity issues were identified during the review.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

Please refer to reviews of other review disciplines.

5. Sources of Clinical Data and Other Information Considered

5.1 Review Strategy

This review focuses on the immunogenicity and safety data from the primary series among subjects who were randomized to receive the 3-dose Imovax Rabies PrEP regimen in Cohort 1 or the 2-dose Imovax Rabies PrEP regimen in Cohort 2 of Study VRV12. Immunogenicity results from subjects assigned to other vaccine groups are included only when relevant to specific hypothesis testing, in accordance with the hierarchical testing framework.

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

The following submissions were reviewed:

- STN 103931/5342.0 Module 2.5 Clinical Overview
- STN 103931/5342.0 Module 2.7 Clinical Summary
- STN 103931/5342.0 Module 5 Clinical Study Reports
- STN 103931/5342.5009 Module 1.11.3 Clinical Information Amendment
- STN 103931/5342.5009 Module 5 Clinical Study Reports
- STN 103931/5342.5010 Module 1.11.3 Clinical Information Amendment
- STN 103931/5342.5012 Module 1.11.3 Clinical Information Amendment
- STN 103931/5342.5013 Module 1.11.3 Clinical Information Amendment
- STN 103931/5342.5015 Module 5 Clinical Study Reports

6. Discussion of Individual Studies/Clinical Trials

6.1 Clinical Study VRV12

6.1.1 Objectives

The selected objectives relevant to this review are summarized below:

Primary Immunogenicity Objective
To demonstrate that VRVg-2 was non-inferior to Verorab and Imovax Rabies in each age group (pediatric and adult subjects in Cohort 1) when administered as a 3-dose PrEP regimen, in terms of proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL at D42, i.e., 14 days after the third injection.

Secondary Immunogenicity Objectives

1) To demonstrate that the observed proportion of subjects in the VRVg-2 group (overall subjects in Cohort 1) achieving an RVNA titer ≥ 0.5 IU/mL at D42 was at least 99%, with a lower limit of the two-sided 95% CI of at least 97%, only if the primary objective was achieved.
2) To demonstrate that VRVg-2 was non-inferior to Verorab and Imovax Rabies in each age group (pediatric and adult subjects pooled from Cohorts 1 and 2), in terms of proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL at D28, i.e., 21 days after the second injection in the primary series, only if the first secondary immunogenicity objective was achieved.
3) To demonstrate that 2-dose VRVg-2 at D28 was non-inferior to 3-dose Imovax Rabies at D42 in each age group (pediatric and adult subjects, respectively, pooled from Cohorts 1 and 2) in terms of proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL, only if the second secondary immunogenicity objective was achieved.
4) To demonstrate that the observed proportion of subjects in the VRVg-2 group (overall subjects pooled from Cohorts 1 and 2) achieving an RVNA titer ≥ 0.5 IU/mL at D28 was at least 99%, with a lower limit of the two-sided 95% CI of at least 97%, only if the third secondary immunogenicity objective was achieved.
5) To demonstrate that 2-dose Imovax Rabies at D28 was non-inferior to 3-dose Imovax Rabies at D42 in the overall subjects (pooled pediatric and adult subjects

in Cohort 1) in terms of proportion of subjects achieving an RVNA titer ≥ 0.5 IU/mL, only if the fourth secondary immunogenicity objective was achieved.
6) To describe the immune response induced by VRVg-2, Verorab, and Imovax Rabies at D28 and D42 in all age groups (pediatric and adult subjects).

Secondary Safety Objective
To describe the safety profile of VRVg-2, Verorab, and Imovax Rabies vaccines, after each vaccine injection, in each age group (Cohorts 1 and 2).

6.1.2 Design Overview

This is a multi-center, observer-blind, controlled, randomized, Phase 3 clinical trial conducted in Thailand. A total of 1700 healthy subjects were planned to be enrolled in the study, including 505 pediatric subjects aged 1 year to <18 years and 1195 adult subjects aged ≥18 years. There are two cohorts, i.e., Cohorts 1 and 2, involved in this study. Cohort 1 included 1010 subjects, evenly divided between pediatric (n=505) and adult (n=505) participants. Subjects in Cohort 1 were randomized in a 3:1:1 ratio to receive as a primary series a 3-dose PrEP regimen of VRVg-2 (Group 1, n=303), Verorab (Group 2, n=101), or Imovax Rabies (Group 3, n=101) at D0, D7, and D28 within each age group through the IM route. Cohort 2 included 690 adult subjects who were randomized in the same 3:1:1 ratio to receive as a primary series a 2-dose PrEP regimen of either VRVg-2 (Group 4, n=414), Verorab (Group 5, n=138), or Imovax Rabies (Group 6, n=138) at D0 and D7 through the IM route.

6.1.3 Population

The study enrolled approximately 1700 healthy subjects aged ≥ 1 year.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects randomized to Groups 1 and 4 received the investigational product VRVg-2. Subjects in Groups 2 and 5 received Verorab, while those in Groups 3 and 6 received Imovax Rabies. Each 0.5 mL dose across the three vaccines contained rabies virus (Wistar Rabies Pitman Moore/WI-38 1503-3M strain) at a potency of ≥ 2.5 IU.

6.1.6 Sites and Centers

This study was conducted at four centers in Thailand.

6.1.7 Surveillance/Monitoring

Please refer to the clinical reviewer's memo.

6.1.8 Endpoints and Study Success Criteria

Primary Immunogenicity Endpoint

- RVNA titers measured by the Rapid Fluorescent Focus Inhibition test (RFFIT) at D42 for pediatric and adult subjects in Cohort 1.
    - Subjects with an RVNA titer ≥ 0.5 IU/mL (i.e., seroconversion) at D42.

Secondary Immunogenicity Endpoints

- RVNA titers measured by RFFIT at D0 and D28 for subjects in Cohorts 1 and 2, and at D42 for subjects in Cohort 1.
    - Subjects with an RVNA titer ≥ 0.5 IU/mL at D0 and D28 in Cohorts 1 and 2, and at D42 in Cohort 1.
    - Subjects with an RVNA titer ≥ Lower Limit of Quantitation (LLOQ) at D0 and D28 in Cohorts 1 and 2, and at D42 in Cohort 1.

Success criteria for the primary and secondary immunogenicity endpoints are summarized in Section 6.1.9.

Secondary Safety Endpoints

- Occurrence of any unsolicited systemic AEs reported in the 30 minutes after each vaccine injection.
- Occurrence of solicited 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 AEs of special interest (AESIs) within at least 6 months after each vaccination as applicable to Cohorts 1 and 2.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Hypotheses for the Primary Objective

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One page determined to be not releasable: (b)(4)

(b) (4)

The hypothesis for the fifth secondary immunogenicity objective was H_0: $P_{\text{Imovax Rabies at D28 (Group 3)}} - P_{\text{Imovax Rabies at D42 (Group 3)}} \leq -10\%$ vs. H_1: $P_{\text{Imovax Rabies at D28 (Group 3)}} - P_{\text{Imovax Rabies at D42 (Group 3)}} > -10\%$, where $P_{\text{Imovax Rabies at D28}}$ and $P_{\text{Imovax Rabies at D42}}$ were the seroconversion rates assessed at D28 and D42 for Imovax Rabies, respectively. The 2-dose Imovax Rabies was considered by the applicant as non-inferior to the 3-dose Imovax Rabies only if H_0 was rejected at a one-sided 2.5% level of alpha. Additionally, the hypothesis was tested against a -5% margin as a supplemental non-inferiority analysis.

Reviewer Comments:

- *In response to regulatory feedback dated December 9, 2022, under STN 103931/5296, the applicant proposed in IND 15026.106 to include the third and the fifth secondary objectives with a non-inferiority margin of -10%. CBER did not agree with the proposed -10% margin and recommended a non-inferiority margin of -5%. This feedback was communicated to the applicant on May 22, 2023. However, in the updated clinical study protocol for Study VRV12 submitted under amendment 111 of IND 15026, the applicant did not address the request for the non-inferiority margin and implemented the margin of -10%. Subsequently, a follow-up comment was sent to the applicant on November 2, 2023, reiterating CBER's recommendation and position. In a response submitted under amendment 113 of IND 15026, the applicant confirmed that a pre-specified supplementary analysis using the -5% non-inferiority margin for the third and the fifth secondary objective has been added, which was incorporated into the Statistical Analysis Plan (SAP) submitted earlier under amendment 112 of IND 15026.*
- *The applicant requested an end-of-phase 2 Type B meeting under amendment 70 of IND 15026, which was held on November 15, 2018. In CBER's pre-meeting written responses to the applicant's questions, dated November 9, 2018, the applicant was informed that demonstrating non-inferiority to Verorab in Study VRV12 was not required for the study's success to support licensure, as Verorab was not licensed in the U.S. In response, the applicant included language in the protocol indicating that non-inferiority to Verorab is not a requirement for study success. Therefore, the success of Study VRV12 did not depend on test results involving Verorab.*

Statistical Methods

All hypotheses listed above involving seroconversion rates assessed at either D42 or D28 were tested using the lower limit of the two-sided 95% CI. Specifically, CIs for single proportions were constructed using the Clopper–Pearson exact method, while CIs for differences between two proportions were calculated using the Wilson score method without continuity correction except for the fifth secondary objective, where the CI was estimated using a generalized linear model (GLM) for repeated measures with a binary response, employing an identity link function under the assumption of a binomial

distribution. If the model failed to converge, the Mover Wilson score method[1] for paired binomial proportions was used to estimate the CI.

Descriptive statistics for RVNA titers were presented using geometric means with the corresponding 95% CIs derived from the Student's t-distribution on the log10-transformed scale. RVNA titers below the LLOQ were imputed as LLOQ/2. For safety outcomes, observed proportions and their corresponding 95% CIs calculated by the Clopper–Pearson exact method were presented.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Four analysis sets were defined for the immunogenicity analyses: the Per-Protocol Analysis Set (PPAS) for D42 and the PPAS for D28 for the primary analyses, and the Full Analysis Set (FAS) and the Full Analysis Set for Immunogenicity (FASI) for the supplementary analyses. All data were analyzed according to the randomized vaccine group in the primary series.

The FAS was defined as the subset of randomized subjects who received at least 1 dose of the study vaccine in the primary series. The FASI, as a subset of FAS, included subjects with a baseline RVNA titer below 0.5 IU/mL. The PPAS for D42, used to assess the primary objective for subjects in Cohort 1, was a subset of the FAS excluding subjects with major protocol deviations before D42, including failure to complete the 3-dose schedule or having an RVNA titer ≥ 0.2 IU/mL at D0. The PPAS for D28 was defined for subjects in Cohorts 1 and 2 and was used for secondary non-inferiority objective evaluations at D28, which included subjects in the FAS excluding those who did not complete a 2-dose schedule at D0 and D7, those with RVNA titer ≥ 0.2 IU/mL at D0, and those with other major protocol deviations before D28.

For the analysis of safety in the primary series, the Safety Analysis Set (SafAS) was defined for each dose as the subset of subjects who received that specific dose. All subjects had their safety analyzed after each dose according to the study vaccine they actually received, and after any dose according to the study vaccine received at the first dose.

A total of 1708 subjects were randomized, of whom 1706 (99.9%) received at least 1 dose of the study vaccines and were included in the FAS and SafAS. No participants received the incorrect vaccine. Two subjects (1 pediatric subject in Group 2 and 1 adult subject in Group 4) did not receive any study vaccine during the primary series and were excluded from the analysis sets. Additionally, a total of 1517 subjects (88.8%) were included in the FASI, while 1434 subjects (84.0%, Cohorts 1 and 2) were included in the PPAS for Day 28. Among the 1010 randomized subjects in Cohort 1, a total of 850

[1] Fagerland, Morten W., Stian Lydersen, and Petter Laake. Recommended tests and confidence intervals for paired binomial proportions. *Statistics in medicine* 33, No. 16 (2014): 2850-2875.

subjects (84.2%) were included in the PPAS for Day 42. Detailed sample size for each randomized group by age group is presented in Table 1 below.

Table 1. Sample Size of Analysis Sets by Randomized Group

Age Group	Analysis Dataset	Group 1 VRVg-2 n (%)	Group 2 Verorab n (%)	Group 3 Imovax Rabies n (%)	Group 4 VRVg-2 n (%)	Group 5 Verorab n (%)	Group 6 Imovax Rabies n (%)	All n (%)
Overall	-	N=607	N=203	N=200	N=420	N=139	N=139	N=1708
-	FAS/SafAS	607 (100)	202 (99.5)	200 (100)	419 (99.8)	139 (100)	139 (100)	1706 (99.9)
-	FASI	553 (91.1)	178 (87.7)	173 (86.5)	361 (86.0)	122 (87.8)	130 (93.5)	1517 (88.8)
-	PPAS for D42	519 (85.5)	169 (83.3)	162 (81.0)	-	-	-	850 (84.2)
-	PPAS for D28	519 (85.5)	169 (83.3)	160 (80.0)	342 (81.4)	120 (86.3)	124 (89.2)	1434 (84.0)
Pediatric	-	N=305	N=100	N=100	-	-	-	N=505
-	FAS/SafAS	305 (100)	99 (99.0)	100 (100)	-	-	-	504 (99.8)
-	FASI	286 (93.8)	90 (90.0)	91 (91.0)	-	-	-	467 (92.5)
-	PPAS for D42	265 (86.9)	85 (85.0)	83 (83.0)	-	-	-	433 (85.7)
-	PPAS for D28	266 (87.2)	86 (86.0)	81 (81.0)	-	-	-	433 (85.7)
Adult	-	N=302	N=103	N=100	N=420	N=139	N=139	N=1203
-	FAS/SafAS	302 (100)	103 (100)	100 (100)	419 (99.8)	139 (100)	139 (100)	1202 (>99.9)
-	FASI	267 (88.4)	88 (85.4)	82 (82.0)	361 (86.0)	122 (87.8)	130 (93.5)	1050 (87.3)
-	PPAS for D42	254 (84.1)	84 (81.6)	79 (79.0)	-	-	-	417 (82.6)
-	PPAS for D28	253 (83.8)	83 (80.6)	79 (79.0)	342 (81.4)	120 (86.3)	124 (89.2)	1001 (83.2)

n: number of subjects fulfilling the item listed; N: number of available subjects in each age group. For items reported by the age group, percentages were based on N. An exception applies to the PPAS for Day 42 dataset, where denominators were based on the total number of available subjects in Cohort 1 only: specifically, 1010 for the overall and 505 for both the pediatric and adult groups.

Source: Table 7 of the interim clinical study report for Study VRV12.

6.1.10.2 Demographics for Imovax Rabies

Demographics of subjects randomized to receive Imovax Rabies (Groups 3 and 6) in the primary series are presented in Table 2 by randomized and age group in the FAS/SafAS.

Table 2. Baseline Demographics by Randomized and Age Group – FAS/SafAS

Demographics	Group 3 (Overall) 3-dose Imovax Rabies (N=200)	Group 3 (Pediatric) 3-dose Imovax Rabies (N=100)	Group 3 (Adult) 3-dose Imovax Rabies (N=100)	Group 6 (Adult) 2-dose Imovax Rabies (N=139)
Age (years)	-	-	-	-
Mean (SD)	22.4 (16.1)	8.6 (4.3)	36.2 (10.7)	37.3 (10.9)
Min, Max	1; 71	1; 17	20; 71	18; 63
Median	18.5	8.0	34.5	38.0
Age Group: n (%)	-	-	-	-
Pediatric (< 18 years)	100 (50.0)	100 (100.0)	-	-
12 to 23 months	2 (1.0)	2 (2.0)	-	-
2 to 11 years	68 (34.0)	68 (68.0)	-	-
12 to 17 years	30 (15.0)	30 (30.0)	-	-
Adult (≥ 18 years)	100 (50.0)	-	100 (100.0)	139 (100)
18 to 40 years	69 (34.5)	-	69 (69.0)	82 (59.0)
41 to 64 years	29 (14.5)	-	29 (29.0)	57 (41.0)
≥ 65 years	2 (1.0)	-	2 (2.0)	0 (0.0)
Sex: n (%)	-	-	-	-
Male	78 (39.0)	54 (54.0)	24 (24.0)	41 (29.5)

Demographics	Group 3 (Overall) 3-dose Imovax Rabies (N=200)	Group 3 (Pediatric) 3-dose Imovax Rabies (N=100)	Group 3 (Adult) 3-dose Imovax Rabies (N=100)	Group 6 (Adult) 2-dose Imovax Rabies (N=139)
Female	122 (61.0)	46 (46.0)	76 (76.0)	98 (70.5)
Sex ratio: Male/Female	0.64	1.17	0.32	0.42

n: number of subjects fulfilling the item listed; N: number of available subjects in each age group. SD: standard deviation. For items reported by the age group, percentages are based on N.

Source: Table 9 of the interim clinical study report for Study VRV12.

The overall mean age in Group 3 was 22.4 ± 16.1 years, younger than in Group 6 (37.3 ± 10.9 years), due to 50% of subjects in Group 3 being pediatric. Most pediatric subjects in Group 3 were aged 2 to 11 years, while the majority of adults in both groups were aged 18 to 40 years. At the extremes, only two pediatric subjects aged 12 to 23 months and two adults aged ≥ 65 years were enrolled in Group 3. A sex imbalance was observed: the male-to-female ratio was 0.64 in Group 3 and 0.42 in Group 6. Among adult subjects in Group 3, there were 24 males vs. 76 females (ratio of 0.32). However, this imbalance was not expected to affect the evaluation of the immunogenicity objectives, as no comparisons between Groups 3 and 6 were made. Of note, as the trial was conducted in Thailand, all subjects identified as Asian and Not Hispanic or Latino.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoint

Based on the PPAS for Day 42, success criteria comparing the 3-dose VRVg-2 (Group 1) to both 3-dose Verorab (Group 2) and 3-dose Imovax Rabies (Group 3) in terms of the D42 seroconversion rates were met, as shown in Table 3. Specifically, the lower limits of the 95% CIs for the differences in the D42 seroconversion rates were above the pre-specified margin of -5% for both pediatric and adult age groups. For VRVg-2 versus Verorab, the lower limits were -1.4% for pediatrics and -0.6% for adults. For VRVg-2 versus Imovax Rabies, the lower limits were -1.4% for pediatrics and -1.5% for adults. Similar results were observed based on the FASI and FAS.

Table 3. Seroconversion Rates for VRVg-2 Versus Verorab and Imovax Rabies at D42 by Age Group – PPAS for D42

Age Group	Group 1 VRVg-2 (N=519)	Group 2 Verorab (N=169)	Group 3 Imovax Rabies (N=162)	Group 1- Group 2	Group 1- Group 3
-	n/M (%) 95% CI	n/ M (%) 95% CI	n/ M (%) 95% CI	Difference (%) 95% CI	Difference (%) 95% CI
Pediatric (< 18 years)	265/265 (100) (98.6, 100)	85/85 (100) (95.8, 100)	83/83 (100) (95.7, 100)	0 (-1.4, 4.3)	0 (-1.4, 4.4)
Adult (≥ 18 years)	254/254 (100) (98.6, 100)	83/84 (98.8) (93.5, 100)	79/79 (100) (95.4, 100)	1.2 (-0.6, 6.4)	0 (-1.5, 4.6)

n: number of seroconverted subjects; M: number of subjects with available data for the endpoint in each age group; N: total number of subjects in the PPAS for D42, including both pediatric and adult subjects.

Source: Table 11 of the interim clinical study report for Study VRV12.

6.1.11.2 Analyses of Secondary Endpoints

The First Secondary Endpoint
(b) (4)

The Second Secondary Endpoint
(b) (4)

(b) (4)

The Third Secondary Endpoint
(b) (4)
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The Fourth Secondary Endpoint
(b) (4)

(b) (4)

Reviewer's comment: (b) (4) *. However, based on the WRO to the Type C meeting request under STN 103931/5333, the review team agreed to allow the applicant to proceed with this supplement. This decision was based on the rationale that the fourth secondary immunogenicity objective for VRVg-2 was not directly relevant to the current sBLA submission, which focuses on the non-inferiority assessment of the 2-dose Imovax Rabies PrEP regimen as defined in the fifth secondary objective. Accordingly, the fifth secondary endpoint, which served as the key and sole objective of this sBLA, would be tested as follows.*

The 5th Secondary Endpoint

Due to the different numbers of participants included in the PPAS for D28 and D42 for Group 3 (160 and 162, respectively), and the lack of convergence in the GLM estimate caused by a 100% seroconversion rate at D42 (162/162), the Mover Wilson score test was used to assess non-inferiority. Specifically, this analysis was conducted on the 160 subjects who had observations recorded at both D28 and D42, including all pediatric and adult participants. Non-inferiority of the seroconversion rate after two doses of Imovax Rabies at D28 as compared to after three doses of Imovax Rabies at D42 in the overall Group 3 population was demonstrated, as the lower limit of the 95% CI for the difference in seroconversion rates was greater than -5%. The estimates, along with those based on the FASI and FAS analysis sets, are presented in Table 5.

Table 5. Seroconversion Rates for Imovax Rabies at D28 and D42 (Group 3 in Cohort 1) – PPAS, FASI, and FAS

Analysis Dataset	Group 3 Imovax Rabies at D28	Group 3 Imovax Rabies at D42	Group 3 at D28 - Group 3 at D42
-	n/M (%) 95% CI	n/ M (%) 95% CI	Difference (%) 95% CI
PPAS	158/160 (98.8) (95.6, 99.8)	160/160 (100) (97.7, 100)	-1.3 (-4.4, 1.3)
FASI	168/170 (98.8) (95.8, 99.9)	170/170 (100) (97.9, 100)	-1.2 (-4.2, 1.2)
FAS	193/195 (99.0) (96.3, 99.9)	195/195 (100) (98.1, 100)	-1.0 (-3.7, 1.0)

n: number of seroconverted subjects; M: number of subjects with available data for the endpoint at both D28 and D42.
Source: Adapted from Table 16, Table 8.2.17, and Table 8.2.18 of the interim clinical study report for Study VRV12.

Immune Response Induced by Imovax Rabies at D28 and at D42 in All Age Groups

The final secondary objective of this review focused on summarizing the immune response induced by Imovax Rabies at D28 and D42 in the overall population and pediatric and adult age groups. Descriptive statistics were used to assess the proportion of participants in each age group who achieved an RVNA titer ≥ 0.2 IU/mL (LLOQ) or ≥ 0.5 IU/mL (i.e., the seroconversion rate), along with corresponding geometric mean titers (GMTs). Detailed results were presented in Table 6 based on the PPAS for D28 and D42.

The presented results for D28 were based on the PPAS for D28 to include Group 6. Of note, identical results for Group 3 could also be obtained from the PPAS for D42.

Table 6. Immunogenicity Response Induced by Imovax Rabies at D28 and D42 – PPAS for D28 and PPAS for D42

Time	Statistics	Group 3 (overall)	Group 3 (Pediatric)	Group 3 (Adult)	Group 6 (Adult)	Groups 3+6 (overall)	Groups 3+6 (Adult)
Post-dose 2 (D28)	# Subjects with available RVNA titer	160	81	79	124	284	203
-	# Subjects with RVNA titer ≥ 0.2 IU/mL (%) (95% CI)	160 (100.0) (97.7, 100)	81 (100.0) (95.5, 100)	79 (100.0) (95.4, 100)	122 (98.4) (94.3, 99.8)	282 (99.3) (97.5, 99.9)	201 (99.0) (96.5, 99.9)
-	# Subjects with RVNA titer ≥ 0.5 IU/mL (%) (95% CI)	158 (98.8) (95.6, 99.8)	81 (100.0) (95.5, 100)	77 (97.5) (91.2, 99.7)	119 (96.0) (90.8, 98.7)	277 (97.5) (95.0, 99.0)	196 (96.6) (93.0, 98.6)
-	GMT (95% CI)	5.13 (4.48, 5.87)	7.48 (6.50, 8.62)	3.48 (2.84, 4.26)	3.91 (3.25, 4.70)	4.56 (4.08, 5.09)	3.74 (3.26, 4.28)
Post-dose 3 (D42)	# Subjects with available RVNA titer	162	83	79	-	-	-
-	# Subjects with RVNA titer ≥ 0.2 IU/mL (%) (95% CI)	162 (100.0) (97.7, 100)	83 (100.0) (95.7, 100)	79 (100.0) (95.4, 100)	-	-	-
-	# Subjects with RVNA titer ≥ 0.5 IU/mL (%) (95% CI)	162 (100.0) (97.7, 100)	83 (100.0) (95.7, 100)	79 (100.0) (95.4, 100)	-	-	-
-	GMT (95% CI)	16.4 (14.7, 18.3)	21.6 (18.7, 25.0)	12.2 (10.6, 14.1)	-	-	-

n: number of subjects who experiencing the endpoint listed; M: number of subjects with available data for the endpoint.
Source: Adapted from Table 17 and Table 18 of the interim clinical study report for Study VRV12.

All subjects in the two PPAS datasets had baseline RVNA titers below the LLOQ. At D28, the seroconversion rate was 158/160 (98.8%) in Group 3 and 119/124 (96.0%) in Group 6. A total of 7 (out of 203) adult participants did not achieve an RVNA titer ≥ 0.5 IU/mL following two doses of Imovax Rabies across Groups 3 and 6. Further, 2 out of the 7 did not achieve an RVNA titer above LLOQ. After three doses of Imovax Rabies, all participants in Group 3, including both pediatric and adult subjects, seroconverted at D42.

In terms of GMTs, adult participants had similar immune responses between the two groups at D28. The GMT in Group 3 adults was 3.48 with 95% CI of (2.84, 4.26) and the GMT in Group 6 was 3.91 with 95% CI of (3.25, 4.70). Higher D28 GMT was observed among pediatric subjects in Group 3 than adults, with a mean of 7.48 and 95% CI (6.50, 8.62). This pattern persisted at D42 in Group 3, where the GMT was 21.6 with 95% CI (18.7, 25.0) in pediatric subjects versus 12.2 with 95% CI (10.6, 14.1) in adults. Nevertheless, GMTs in all groups were higher than the seroconversion threshold of 0.5 IU/mL.

Of note, similar results were observed in analyses based on the FASI analysis set. While the FAS included participants with baseline RVNA titers greater than or equal to the LLOQ, resulting in slightly higher GMTs compared to the other two analysis sets, the overall response patterns remained consistent.

6.1.11.3 Subpopulation Analysis

The key fifth secondary objective was evaluated separately for pediatric and adult participants. Among those in Group 3 with observations at both Day 28 and Day 42 in PPAS, the difference in seroconversion rates between the 2-dose and 3-dose Imovax Rabies was 0% with 95% CI (-4.5%, 4.5%) for pediatrics and -2.5% with 95% CI (-8.8%, 2.5%) for adults. While the lower limit of the 95% CI for the pediatric group was greater than -5%, the adult group would not have met a non-inferiority margin of -5%. Of note, the study was not powered to assess non-inferiority within age groups. These findings were consistent by analyses using the FASI and FAS.

Additionally, there was a consistent decreasing trend in GMTs with increasing age subgroups from 12–23 months, 2–11 years, to 12–17 years in the pediatric population, and from 18–40 years, 41–64 years, to ≥65 years in adults. However, as noted previously, no patterns were observed in seroconversion rates or GMTs when comparing female and male participants.

6.1.12 Safety Analyses

A summary of solicited reactions within 7 days after any Imovax Rabies injection during the primary series in subjects randomized to Groups 3 and 6 is presented in Table 7 based on the SafAS dataset.

Overall, 126/200 (63.0%) of subjects in Group 3, who received three doses of Imovax Rabies, reported at least one solicited reaction within 7 days of any injection. This rate was higher than the 47/139 (33.8%) observed in Group 6, where participants received two doses. Within Group 3, the incidence of any solicited reactions was slightly higher in pediatric subjects than in adults (68.0% vs. 58.0%). However, the rates of each reaction were generally similar between the age groups. Consistent with the overall trend, adults in Group 3 experienced a higher rate of solicited reactions than adults in Group 6.

The most frequently reported injection site reaction was tenderness/pain, occurring in 53.0% of Group 3 and 30.9% of Group 6 participants. Myalgia was the most common systemic reaction, reported by 39.4% of Group 3 and 20.9% of Group 6 participants, followed by malaise and headache. Only one case of a Grade 3 solicited reaction was reported: a pediatric subject in Group 3 experienced Grade 3 malaise and myalgia post first injection. Of note, in Group 3, two pediatric subjects aged 12 to 23 months were assessed for vomiting, abnormal crying, drowsiness, loss of appetite, and irritability as solicited systemic reactions, in place of headache, malaise, and myalgia. Fever was also collected. One of the two participants reported crying and vomiting after receiving the

third dose of Imovax Rabies with mild severity. Among the 173 subjects who reported solicited reactions, 9.2% (16 out of 173) experienced at least one solicited reaction lasting more than 3 days.

Table 7. Solicited Reactions Within 7 days After Any Imovax Rabies Vaccine Injection – FAS/SafAS

Subjects experiencing at least one:	Group 3 (Overall) 3-dose Imovax Rabies (N=200)	Group 3 (Pediatric) 3-dose Imovax Rabies (N=100)	Group 3 (Adult) 3-dose Imovax Rabies (N=100)	Group 6 (Adult) 2-dose Imovax Rabies (N=139)
-	n (%)	n (%)	n (%)	n (%)
Solicited reaction	126 (63.0)	68 (68.0)	58 (58.0)	47 (33.8)
Grade 3 solicited reaction	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Solicited injection site reaction	107 (53.5)	55 (55.0)	52 (52.0)	43 (30.9)
Grade 3 injection site reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site tenderness/pain	106 (53.0)	54 (54.0)	52 (52.0)	43 (30.9)
Injection site erythema	6 (3.0)	6 (6.0)	0 (0.0)	1 (0.7)
Injection site swelling	13 (6.5)	9 (9.0)	4 (4.0)	1 (0.7)
Solicited systemic reaction	93 (46.5)	45 (45.0)	48 (48.0)	33 (23.7)
Grade 3 systemic reaction	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Fever	4 (2.0)	3 (3.0)	1 (1.0)	0 (0.0)
Headache	46 (23.3)	24 (24.5)	22 (22.0)	8 (5.8)
Malaise	48 (24.2)	23 (23.5)	25 (25.0)	12 (8.6)
Myalgia	78 (39.4)	37 (37.8)	41 (41.0)	29 (20.9)

n: number of subjects experiencing the endpoint listed; N: number of available subjects in each age group. Percentages were based on the N for each age group. An exception applies to headache, malaise, and myalgia, for which the denominators were based on the total number of available subjects aged over 23 months. Specifically, 198 for the overall group, 98 for the pediatric group, and 100 for the adult group.

Source: Adapted from Tables 23, 25, and 8.3.2 of the interim clinical study report for Study VRV12.

Reviewer's comment: During the review process, the data standards reviewer, Dr. Brenda Baldwin, identified a potential non-compliance issue regarding the diary data recorded in the STDM.FACE dataset for both the VAJ00001 and VRV12 studies. Specifically, for Study VAJ00001, only records from subjects who had at least one day of diary data reported were included in the dataset. In addition, 87.5% of entries regarding diary responses were left as blank in the FACE dataset for Study VRV12. In response to Information Requests (IRs) #11 and #13, submitted under STN 103931/5342.5010 and STN 103931/5452.5012, respectively, the applicant clarified that the solicited reactions reported in the two clinical study reports were based on the SDTM.CE dataset, which reflects responses to questions listed in the Case Report Form (CRF) and completed by investigators. However, the subject-level compliance with diary data cannot be assessed solely based on the available datasets. To ensure that data are accurately described, the applicant has proposed language in the package insert outlining the procedure for monitoring and assessing solicited reactions during the study, as requested.

As shown in Table 8, no immediate unsolicited AEs or ARs, defined as AEs related to the vaccination, were reported within 30 minutes after any vaccine injection. For unsolicited AEs collected up to 28 days following any vaccine injection, the incidence rates were 40 out of 200 (20.0%) in Group 3 and 12 out of 139 (8.6%) in Group 6. One pediatric participant experienced a severe unsolicited AE (Grade 3), which was determined to be

unrelated to the vaccination by the investigator. Of note, one unsolicited AE in Group 6 led to study discontinuation due to suspected rabies exposure following the second dose. Additionally, a total of 5 participants (2.5%) in Group 3, including 3 pediatric and 2 adult participants, reported SAEs within 6 months after the last vaccination. None of the SAEs in Group 3 were considered by the investigator as related to the vaccination. No deaths and AESIs were reported in this study.

Table 8. Unsolicited AEs After Any Imovax Rabies Vaccine Injection – FAS/SafAS

Period/ Subjects experiencing at least one after any vaccine injections:	Group 3 (Overall) 3-dose Imovax Rabies (N=200)	Group 3 (Pediatric) 3-dose Imovax Rabies (N=100)	Group 3 (Adult) 3-dose Imovax Rabies (N=100)	Group 6 (Adult) 2-dose Imovax Rabies (N=139)
-	n (%)	n (%)	n (%)	n (%)
Within 30 minutes	-	-	-	-
Immediate unsolicited AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immediate unsolicited AR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Up to 28 days	-	-	-	-
Unsolicited AE	40 (20.0)	14 (14.0)	26 (26.0)	12 (8.6)
Grade 3 unsolicited AE	1 (0.5)	1 (1.0)	0 (0.0)	0 (0.0)
Unsolicited AR	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Grade 3 unsolicited AR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Until 6 months after last vaccination	-	-	-	-
SAE	5 (2.5)	3 (3.0)	2 (2.0)	0 (0.0)

n: number of subjects experiencing the endpoint listed; N: number of available subjects in each age group. Percentages were based on the N for each age group.

Source: Adapted from Tables 31, 33, 34, 8.3.46 of the interim clinical study report for Study VRV12.

7. Integrated Overview of Efficacy

Not applicable.

8. Integrated Overview of Safety

Not applicable.

9. Additional Statistical Issues

There were no additional statistical issues.

10. Conclusions

No major statistical issues were identified in the immunogenicity and safety results that would affect conclusions regarding the 2-dose Imovax Rabies PrEP regimen. The key fifth secondary objective was met, demonstrating non-inferiority of the 2-dose Imovax Rabies regimen compared to the 3-dose Imovax Rabies regimen in terms of seroconversion rates, although the fourth secondary objective (b) (4) . The lower limit of the 95% CI for the difference in seroconversion rates between the two regimens was -4.4%,

which was higher than the pre-specificied non-inferiority margin of -10% and -5%. The overall data support inclusion of the 2-dose PrEP immunization schedule for Imovax Rabies.