Application Type	Original BLA
STN	125777/0
CBER Received Date	December 22, 2022
PDUFA Goal Date	November 22, 2023
Division / Office	DVRPA/OVRR
Committee Chair	Sudhakar Agnihothram
Clinical Reviewer(s)	Sixun Yang
Project Manager	Konstantin Virnik Georgeta Crivat
Priority Review	Yes
Reviewer Name(s)	Ruoxuan Xiang
Review Completion Date / Stamped Date	
Concurrence	Lei Huang Concurring Reviewer, Vaccine Evaluation Branch (VEB), Division of Biostatistics (DB), Office of Biostatistics and Pharmacovigilance (OBPV)
	Tsai-Lien Lin Branch Chief, VEB/DB/OBPV
	John Scott Director, DB/OBPV
Applicant	Valneva Austria GmbH
Established Name	Chikungunya Vaccine, Live-Attenuated , Absorbed
(Proposed) Trade Name	IXCHIQ
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	A dose of (b) (4) $TCID_{50}$ per 0.5 mL of the lyophilized formulation
Dosage Form(s) and Route(s) of Administration	Lyophilized dosage form which is reconstituted with 0.5 mL sterile water for injection
Dosing Regimen	One dose
Indication(s) and Intended Population(s)	Active immunization for the prevention of disease caused by Chikungunya virus in individuals 18 years and above

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1. EXECUTIVE SUMMARY

Valneva, the applicant, submitted an original Biologics License Application (BLA), STN 125777/0, of the live-attenuated Chikungunya virus vaccine for active immunization for the Prevention of Disease Caused by Chikungunya Virus (CHIKV).

The two pivotal clinical studies, VLA1553-301 and VLA1553-302, used a CHIKV micro plaque reduction neutralization test (μPRNT) to evaluate the levels of antibodies that neutralize CHIKV infection. For pivotal study VLA1553-301, the primary immunogenicity endpoint was the proportion of participants with a seroprotective CHIKV antibody level, defined as $\mu PRNT_{50}$ titer ≥ 150 for baseline negative participants 28 days post vaccination, where the cutoff was determined based on a nonhuman primate (NHP) passive transfer study.

This review memo documents the statistical review of the μPRNT assay validation. Overall, the results of this validation showed that the μPRNT is precise, accurate, linear, specific and stable, and the assay is suitable for its intended use to measure virus neutralizing antibodies against CHIKV in human sera.

2. REGULATORY BACKGROUND

The SOP and qualification of the μPRNT assay were submitted to IND 17854.27. The validation protocol of the μPRNT assay was submitted to IND 17854.30, and the initial validation report was submitted to IND 17854.36. CBER sent an information request (IR) comment regarding the report, to which the applicant submitted the responses to IND 17854.48.

On August 11, 2023, FDA issued a Major Amendment acknowledgement letter to the applicant due to a substantial amount of new information in the post-marketing confirmatory trial protocol (b) (4) -402 submitted on July 31, 2023. Therefore, the action due date was extended by three months to November 22, 2023.

3. SOURCES OF DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

3.1 Review Strategy
This clinical assay statistical review focuses on the μPRNT assay used for the evaluation of the immunogenicity endpoints in the pivotal studies.

3.2 BLA/IND Documents That Serve as the Basis for the Statistical Review
The following submissions were reviewed:

- STN 125777/0.3 Module 2.7 Clinical Summary
- STN 125777/0.3 Module 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

4. DISCUSSION OF INDIVIDUAL STUDIES

4.1 Validation Report for CHIKV Micro-PRNT

The method validation for CHIKV micro plaque reduction neutralization test (µPRNT) in human serum assessed the following performance parameters: Precision, Dilutional Linearity/Relative Accuracy, Lower/Upper Limit of Quantification, Specificity, Freeze/Thaw stability, Robustness, and Comparability of Human and NHP Serum. A summary of the acceptance criteria and validation results are provided in Table 1.

(b) (4)

6 pages determined to be not releasable: (b)(4)

(b) (4)

5. CONCLUSIONS

There were no major statistical issues identified in the validation report of the μPRNT assay. I consider this assay to be suitable for its intended use to measure virus neutralizing antibodies against CHIKV in human sera.