Statistical Review and Evaluation	
Application Type	BLA (Efficacy supplement)
STN	125690/55
CBER Received Date	6/27/2022
PDUFA Goal Date	4/27/2023
Division / Office	Division of Vaccines and Related Product Applications (DVRPA)/ Office of Vaccines Research and Review (OVRR)
Committee Chair	Stephanie Polo
Clinical Reviewer	Omolara Adewuni
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Priority Review	No
Reviewer Name(s)	Sang Ahnn, VEB/DB/OBPV
Supervisory Concurrence	Lei Huang, Concurring Reviewer, VEB/DB/OBPV Tsai-Lien Lin, Branch Chief, VEB/DB/OBPV
Applicant	Merck Sharp & Dohme Corp.
Established Name	Ebola Zaire Vaccine, Live
Trade Name	ERVEBO®
Pharmacologic Class	Vaccine
Formulation	1 mL suspension for injection supplied as a single-dose vial
Dosage Form(s) and Route(s) of Administration	A single 1 mL dose, intramuscular injection
Indication(s) and Intended Population(s)	Indicated for the prevention of disease caused by Zaire ebolavirus in individuals 1 year of age and older

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1. Executive Summary

V920 Ebola vaccine (rVSV-ZEBOV) is a recombinant, replication-competent vesicular stomatitis virus-based vaccine expressing a surface glycoprotein of Zaire Ebolavirus. The vaccine is a genetically engineered, attenuated live vaccine. The established name of the vaccine is Ebola Zaire Vaccine, Live.

FDA approved this vaccine on December 19, 2019 for individuals 18 years of age and older (trade name ERVEBO®). This submission, which is the *Required Pediatric Assessment* in accordance with PMR#1 for ERVEBO®, includes the applicant's clinical study report (CSR) of a Phase 2, randomized, double-blind, placebo-controlled study [referred to as Partnership for Research on Ebola VACcination (PREVAC) study hereafter] of three vaccine strategies: Ad26.ZEBOV/MVA-BN-Filo vaccine (Janssen), and V920 (ERVEBO® by Merck) with or without a boost at 56 days in children ≥1 year of age and adults. The CSR included in this submission presents immunogenicity and safety results from only the ERVEBO® and placebo groups.

The applicant is seeking an indication expansion of ERVEBO® for the prevention of disease caused by Zaire ebolavirus to include individuals 1 year of age and older based on the above PREVAC study by demonstrating non-inferior immunogenicity of ERVEBO® in children 1 to 17 years of age compared with adults for antibody responses (GP-ELISA GMT) on Day 28 after the first vaccination and on Month 12 after the final vaccination.

PREVAC study

The Partnership for Research on Ebola VACcination (PREVAC) study is a randomized, double-blind, placebo-controlled phase 2 clinical trial of three vaccine strategies against the Ebola virus in healthy volunteers 1 year of age and above. The three vaccine strategies are V920 (ERVEBO® by Merck) with or without a booster dose at 56 days, and the Ad26.ZEBOV/MVA-BN-Filo vaccine (Janssen) regimen with Ad26.ZEBOV given as the first dose and the MVA-BN-Filo vaccine given 56 days later.

There have been 4 versions of the protocol with those enrolled in Version 4.0 comprising the primary analysis cohort. Also, since the applicant (Merck) is seeking an age extension in the package insert (*from* individuals 18 years of age and older *to* individuals 1 year of age and older) for ERVEBO®, the CSR in this submission includes immunogenicity and safety results of only V920 (ERVEBO®) and placebo. The primary immunogenicity objective is to demonstrate that V920 (pooled V920 group) is noninferior in children 1 to 17 years of age compared with adults for antibody response (GP-ELISA GMT) on Day 28 after randomization (first vaccination).

Participants were enrolled at 6 sites in four countries (Guinea, Liberia, Sierra Leone, and

Mali). Under Protocol Version 4, a total of 1602 participants were randomized to the V920 1-dose (n=802), V920 2-dose (n=399) or placebo (n=401) groups. A total of 1551 participants (V920 1-dose (n=772), V920 2-dose (n=389), placebo (n=390)) were included in the GP-ELISA Per-Protocol Immunogenicity Population. As shown in Table 1 below, V920 (pooled V920 group) is noninferior in children 1 to 17 years of age compared with adults for antibody response (GP-ELISA GMT) on Day 28 after randomization (first vaccination), as the GMT ratio (i.e. GMT_{1-17}/GMT_{18+}) is 1.42 with 2-sided 95% CI of (1.24, 1.62), where the lower limit of the CI is above the prespecified non-inferiority margin of 0.5.

Table 1. Analysis of pooled V920 (1-dose & 2-dose groups combined) in children aged 1 to 17 years vs. adults based on Day 28 GP-ELISA geometric mean titers (GMT): GP-ELISA Per-Protocol immunogenicity population – Protocol Version 4.

Age	**Baseline** n GMT (95% CI)	**Day 28** n GMT (95% CI)	**Month 12** n GMT (95% CI)
1 to 17 years of age	529 99.6 EU/mL (91.6, 108.2)	499 1748.8 EU/mL (1585.6, 1928.7)	423 1579.1 EU/mL (1443.2, 1727.7)
18+ years	570 138.2 EU/mL (129.2, 147.9)	519 1234.4 EU/mL (1132.5, 1345.4)	436 1070.8 EU/mL (985.6, 1163.4)

n = number of participants contributing to the analysis.
Source: Adapted from the applicant's Tables 14.2-37 and -38 in the CSR of PREVAC study.

Non-inferior immunogenicity in children 1 to 17 years of age compared with adults is also shown in each of the two dose groups (1-dose & 2-dose groups) respectively.

V920 (1- and 2-dose) was generally well tolerated in participants 1 year of age and older. Five children [3 (0.7%) in the 1-dose V920 group, 2 (0.5%) in the placebo group] and 4 adults [3 (0.7%) in the 1-dose V920 group, 1 (0.2%) in the placebo group] died during the study. No death occurred in the 2-dose V920 group. None of the SAEs or deaths were considered related to study intervention by the investigator/applicant.

The data presented in this application appears to support the applicant's proposed indication expansion.

2. Clinical and Regulatory Background

Please refer to this section in the clinical reviewer's review.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

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

3.2 Compliance with Good Clinical Practices and Data Integrity

No data integrity issue was found.

5. Sources of Clinical data and Other Information Considered in the Review

5.1 Review Strategy

This submission includes the clinical study report of Partnership for Research on Ebola VACcination (PREVAC) study. Statistical aspects of the immunogenicity and safety analyses were reviewed.

5.2 BLA Documents that Serve as the Basis for the Statistical Review

This application (STN 125690/55) was submitted on 6/27/2022. The Clinical Study Report (CSR), electronic datasets, and Case Report Forms (CRFs) for PREVAC study are in Section 5.3.5.1 of this submission (STN 125690/55.0 and STN 125690/55.4).

6. Discussion of Individual Studies/Clinical Trials

6.1 Partnership for Research on Ebola VACcination (PREVAC) study

Title of the study: "Partnership for Research on Ebola VACcination (PREVAC) study – a randomized, double-blind, placebo-controlled Phase 2 clinical trial evaluating three vaccine strategies against Ebola in healthy volunteers in four West African countries"

Study initiation date: 7/24/2017 (first visit of the first participant)
Study completion date: 12/24/2019 (last visit of the last participant)

6.1.1 Objectives

There have been 4 versions of the protocol with those enrolled in Version 4.0 comprising the primary analysis cohort. Also, since the applicant (Merck) is seeking an age extension in the package insert (*from* individuals 18 years of age and older *to* individuals 1 year of

age and older) for ERVEBO®, the CSR in this submission includes immunogenicity and safety results for only the V920 (ERVEBO®) and placebo groups.

The primary immunogenicity objective is to demonstrate that V920 (pooled V920 group) is noninferior in children 1 to 17 years of age compared with adults for antibody response (GP-ELISA GMT) on Day 28 after randomization (first vaccination).

The primary safety objective is to evaluate the safety and tolerability of V920 through 1-year post-vaccination.

6.1.2 Design Overview

This is a randomized, double-blind, placebo-controlled phase 2 clinical trial of three vaccine strategies against the Ebola virus in healthy volunteers 1 year of age and above. The three vaccine strategies are the rVSVΔG-ZEBOV-GP vaccine, with or without a booster dose at 56 days, and the Ad26.ZEBOV/MVA-BN-Filo vaccine regimen with Ad26.ZEBOV given as the first dose and the MVA-BN-Filo vaccine given 56 days later.

There have been 4 versions of the protocol with those enrolled in Version 4.0 comprising the primary analysis cohort. Under protocol Version 4.0, a total of 2802 healthy volunteers (1401 1-17 years old and 1401 18+ years old) were enrolled at 6 sites in four countries (Guinea at two sites, Liberia, Mali at two sites, and Sierra Leone), and randomized - stratified by sites and age group (1 to 17 years vs. 18+ year) in a 2:1:2:1:1 ratio into 5 groups:

1. Ad26.ZEBOV 0.5 mL (Day 0) / MVA-BN-Filo 0.5 mL (Day 56),
2. Placebo 0.5mL (Day 0) / Placebo 0.5mL (Day 56),
3. V920 1.0 mL (Day 0) / Placebo 1.0mL (Day56),
4. V920 1.0 mL (Day 0) / V920 1.0 mL (Day56), or
5. Placebo 1.0 mL (Day 0) / Placebo 1.0 mL (Day 56).

Since the applicant (Merck) is seeking an age extension in the package insert (*from* individuals 18 years of age and older *to* individuals 1 year of age and older) for ERVEBO® (V920), the CSR in this submission includes immunogenicity and safety results from only the V920 and placebo groups. For immunogenicity, groups 3, 4 and 5 are included for analyses. For safety, groups 2, 3, 4 and 5 are included for analyses.

6.1.3 Population

The primary immunogenicity analysis was performed on the per-protocol immunogenicity population which consists of all vaccinated participants with serology data who had a serum sample collected within an acceptable day range and did not violate inclusion/exclusion criteria. A total of 1551 participants (V920 1-dose (n=772), V920 2-dose (n=389), and placebo 1.0 mL (n=390)) were included in the GP-ELISA Per-Protocol Immunogenicity Population.

Safety was evaluated on the all-participants-as-treated (APaT) safety population. The APaT population consists of all randomized subjects who received at least one dose of study vaccination. Subjects were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population.

6.1.4 Study Treatments or Agents Mandated by the Protocol

1. The 2-dose heterologous vaccination regimen: Ad26ZEBOV vaccine at Day 0 and MVA-BN-Filo at Day 56 (0.5 mL for both doses).
2. Placebo at Day 0 and Placebo at Day 56 (0.5 mL for both doses)
3. V920 / Placebo: rVSV-ZEBOV vaccine (ERVEBO®) at Day 0 and Placebo at Day 56 (1.0 mL for both doses)
4. V920 / V920: rVSV-ZEBOV vaccine (ERVEBO®) at Day 0 and rVSV-ZEBOV vaccine (ERVEBO®) at Day 56 (1.0 mL for both doses)
5. Placebo at Day 0 and Placebo at Day 56 (1.0 mL for both doses)

- The placebo is sterile normal saline (sodium chloride 0.9% for injection, (b) (4) , preservative-free).

6.1.6 Sites and centers

Participants were enrolled at 6 sites in four countries (Guinea at 2 sites, Liberia, Mali at 2 sites, and Sierra Leone). Overall, 36%, 17%, 22% and 25% of enrollees were from Guinea, Liberia, Mali, and Sierra Leone respectively.

6.1.7 Surveillance/Monitoring

Please refer to this section in the clinical reviewer's review.

6.1.8 Endpoints and Criteria for Study Success

Immunogenicity endpoint: The primary immunogenicity endpoint is Ebola virus glycoprotein (GP-EBOV) antibody response at Day 28 after randomization (first vaccination), as measured by GP-ELISA. The secondary Immunogenicity endpoints are (a) Ebola virus glycoprotein (GP-EBOV) antibody response at Month 3 and Month 12 after randomization (first vaccination), as measured by GP-ELISA, and (b) Neutralizing antibody response at Day 28, Month 3, and Month 12 after randomization (first vaccination), as measured by PRNT. The study success criterion based on immunogenicity is that among the recipients of V920 (ERVEBO®; 1-dose and 2-dose groups combined), the lower bound (LB) of the 2-sided 95% confidence interval (CI) of the GMT ratio [GMT of GP-EBOV antibody response at Day 28 as measured by GP-ELISA in children 1 to 17 years of age / GMT of GP-EBOV antibody response at Day 28 as measured by GP-ELISA in adults 18+ years of age] is > 0.5.

Safety endpoints: The primary safety endpoint is SAEs, including death, occurring through Month 12. Other safety endpoints are (a) injection-site reactions and targeted symptoms of any grade severity and Grade 3 or 4 unsolicited AEs after first vaccination and through 7, 14, and 28 days after first vaccination, (b) injection-site reactions and targeted symptoms of any grade severity and Grade 3 or 4 unsolicited AEs after second vaccination, through 7 days after second vaccination (63 days after first vaccination), and through approximately 28 to 35 days after second vaccination (Month 3 after first vaccination).

6.1.9 Statistical Considerations and Statistical Analysis Plan

The primary immunogenicity hypothesis is

H_0: $GMT_{1-17}/GMT_{18+} \leq 0.5$ vs. **H_a:** $GMT_{1-17}/GMT_{18+} > 0.5$

where GMT_{1-17} = geometric mean titer (GMT) of GP-EBOV antibody response at Day 28 as measured by GP-ELISA in children 1 to 17 years of age, and GMT_{18+} = GMT of GP-EBOV antibody response at Day 28 as measured by GP-ELISA in adults 18+ years of age.

Analyses were conducted by log-transforming the data, performing analysis of variance (ANOVA) on the log-transformed data, model, and un-transforming the statistics.

6.1.10 Primary Immunogenicity Analyses

The primary immunogenicity analysis was performed on GP-ELISA per-protocol immunogenicity population which consists of all vaccinated participants with serology data who had a serum sample collected for GP-ELISA within an acceptable day range and did not violate inclusion/exclusion criteria.

A total of 1551 participants (V920 1-dose (n=772), V920 2-dose (n=389), placebo (n=390)) were included in the GP-ELISA Per-Protocol Immunogenicity Population. As shown in Table 2 below, V920 (pooled V920 group) is noninferior in children 1 to 17 years of age compared with adults for antibody response (GP-ELISA GMT) on Day 28 after randomization (first vaccination). The GMT ratio (i.e. GMT_{1-17}/GMT_{18+}) is 1.42 with 2-sided 95% CI of (1.24, 1.62).

Also, as shown in Table 2, antibody response is noninferior in 1 to 17 years of age compared with adults in each of the V920 dose groups (1-dose and 2-dose), respectively. The GMT ratio (i.e. GMT_{1-17}/GMT_{18+}) is 1.47 with 2-sided 95% CI of (1.22, 1.77) for the 1-dose group; the GMT ratio is 1.31 with 2-sided 95% CI of (0.99, 1.75) for the 2-dose group.

Table 2. Analysis of V920 in children aged 1 to 17 years vs. adults based on Day 28 GP-ELISA geometric mean titers (GMT): GP-ELISA Per-Protocol immunogenicity population – Protocol Version 4.

V920 dose group	Age	Baseline n	Baseline GMT (95% CI)	Day 28 n	Day 28 GMT (95% CI)	Month 12 n	Month 12 GMT (95% CI)
1-dose & 2-dose groups combined	1-17 years	529	99.6 EU/mL (91.6, 108.2)	499	1748.8 EU/mL (1585.6, 1928.7)	423	1579.1 EU/mL (1443.2, 1727.7)
	18+ years	570	138.2 EU/mL (129.2, 147.9)	519	1234.4 EU/mL (1132.5, 1345.4)	436	1070.8 EU/mL (985.6, 1163.4)
1-dose group	1-17 years	351	100.3 EU/mL (90.6, 111.1)	336	1823.6 EU/mL (1618.5, 2054.7)	284	1444.4 EU/mL (1295.1, 1610.9)
	18+ years	379	140.2 EU/mL (129.0, 152.4)	343	1241.2 EU/mL (1116.4, 1380.0)	292	1088.4 EU/mL (983.5, 1204.6)
2-dose group	1-17 years	178	98.1 EU/mL (85.0, 113.2)	163	1604.0 EU/mL (1351.5, 1903.8)	139	1894.6 EU/mL (1621.0, 2214.4)
	18+ years	191	134.3 EU/mL (119.5, 151.0)	176	1221.2 EU/mL (1053.2, 1415.9)	144	1035.9 EU/mL (896.6, 1196.9)

n = number of participants contributing to the analysis.
Source: Adapted from the applicant's Tables 14.2-37 and 38 in the CSR of PREVAC study.

6.1.11 Secondary Immunogenicity Analyses

The secondary immunogenicity analysis was performed on plaque reduction neutralization test (PRNT) per-protocol immunogenicity population which consists of all vaccinated participants with serology data who had a serum sample collected for PRNT within an acceptable day range and did not violate inclusion/exclusion criteria.

A total of 821 participants (V920 1-dose (n=412), V920 2-dose (n=206), placebo (n=203)) were included in the PRNT Per-Protocol Immunogenicity Population. As shown in Table 3 below, the PRNT GMTs in children 1 to 17 years of age and in adults ≥18 years of age in the pooled V920 on Day 28 after randomization (first vaccination) are 277.1 and 169.2, respectively.

Table 3. Analysis of pooled V920 (1-dose & 2-dose groups combined) in children aged 1 to 17 years vs. adults based on Day 28 PRNT GMT: PRNT Per-Protocol immunogenicity population – Protocol Version 4.

Age	Baseline n	Baseline GMT (95% CI)	Day 28 n	Day 28 GMT (95% CI)	Month 12 n	Month 12 GMT (95% CI)
1 to 17 years of age	429	17.8 (17.4, 18.2)	399	277.1 (255.8, 300.2)	308	330.9 (305.0, 359.9)
18+ years	132	18.0 (17.2, 18.7)	140	169.2 (147.4, 194.3)	115	139.8 (121.3, 161.1)

n = number of participants contributing to the analysis.
Source: Adapted from the applicant's Tables 14.2-88 and 89 in the CSR of PREVAC study.

6.1.12 Safety Analyses

V920 (1- and 2-dose) was generally well tolerated in participants 1 year of age and older. Five children [3 (0.7%) in the 1-dose V920 group, 2 (0.5%) in the placebo group] and 4 adults [3 (0.7%) in the 1-dose V920 group, 1 (0.2%) in the placebo group] died during the study. No death occurred in the 2-dose V920 group. None of the SAEs or deaths were considered related to study intervention by the investigator/applicant. Please see the clinical review for further discussion on SAEs.

6.1.13 Subgroup Analyses of the Primary Immunogenicity Endpoint

The primary immunogenicity analysis was performed by comparing children aged 1 to 17 years vs. adults, based on Day 28 GP-ELISA geometric mean titers (GMT), and immunogenic noninferiority in children aged 1 to 17 years is shown when compared to adults. Subgroup analyses by sex (male, female) show consistent results in children aged 1 to 17 years compared to adults in each of male and female subgroups: $GMT_{1\text{-}17}/GMT_{18+}$ is 1.42 with 2-sided 95% CI of (1.18, 1.70) for males, and $GMT_{1\text{-}17}/GMT_{18+}$ is 1.43 with 2-sided 95% CI of (1.17, 1.75) for females. Subgroup analysis by race was not performed since information on race had not been collected for this study of which participants were enrolled from Guinea, Liberia, Mali, and Sierra Leone.

7. Integrated Overview of Immunogenicity

N/A

8. Integrated Overview of Safety

N/A

10. Conclusions

1. Immune responses (measured by GP-ELISA) to ERVEBO (V920) were shown to be non-inferior in children 1 to 17 years of age when compared to adults. The applicant's results support immuno-bridging ERVEBO from children to adults (where the clinical efficacy was demonstrated). However, since the association of the level of GMT (measured by GP-ELISA) and protection from the disease has not been established, the immunogenicity results from this study need to be interpreted with caution.

2. V920 (1- and 2-dose) was generally well tolerated in participants 1 year of age and older. Five children [3 (0.7%) in the 1-dose V920 group, 2 (0.5%) in the placebo group] and 4 adults [3 (0.7%) in the 1-dose V920 group, 1 (0.2%) in the placebo group] died during the study. No death occurred in the 2-dose V920 group. None of the SAEs or deaths were considered related to study intervention by the investigator or the applicant.

In conclusion, the data presented in this application appears to support the applicant's proposed indication expansion.