

Summary Basis for Regulatory Action

Date: December 19, 2019

Revised January 29, 2020 to correct the CMC information to be submitted post-licensure

From: Stephanie Polo, Chair of the Review Committee

BLA STN#: 125690/0

Applicant Name: Merck Sharp & Dohme Corp.

Date of Submission: July 15, 2019

Goal Date: March 14, 2020

Proprietary Name/Established Name: ERVEBO/Ebola Zaire Vaccine, Live

Indication: ERVEBO is a vaccine indicated for the prevention of disease caused by *Zaire ebolavirus* in individuals 18 years of age and older.

Limitations of use:

- The duration of protection conferred by ERBEVO is unknown.
- ERVEBO does not protect against other species of *Ebolavirus* or *Marburgvirus*.
- Effectiveness of the vaccine when administered concurrently with antiviral medication, immune globulin (IG) and/or blood or plasma transfusions is unknown.

Recommended Action:

The review committee recommends approval of this product.

Review Office Signatory Authority: Marion Gruber, Director, OVR

☒ I concur with the summary review.

☐ I concur with the summary review and include a separate review to add further analysis.

☐ I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the Summary Basis of Regulatory Action (SBRA).

Document title	Reviewer name, Document date
CMC Reviews • <i>CMC (OVRD/DVP)</i> • <i>Facilities review (OCBQ/DMPQ)</i> • <i>Establishment Inspection Report (OCBQ/DMPQ)</i>	Dmitriy Volokhov, DVM, PhD – December 18, 2019 Richard Lewis, PhD – November 22, 2019 Christian Lynch – December 16, 2019
Clinical Reviews • <i>Clinical (OVRD/DVRPA)</i> • <i>Postmarketing safety epidemiological review (OBE/DE)</i> • <i>BIMO (OCBQ/DIS)</i>	Rebecca Reindel, MD – December 19, 2019 Ravi Goud, MD, MPH – December 12, 2019 Malcolm Nasirah, PharmD, MS – June 7, 2019
Statistical Reviews • <i>Clinical data (OBE/DB)</i> • <i>Non-clinical data (OBE/DB)</i>	Sang Ahnn, PhD – December 18, 2019 Charles (Yinkiu) Cheung, PhD – November 12, 2019
Pharmacology/Toxicology Reviews • <i>Toxicology and Developmental toxicology (OVRD/DVRPA)</i> • <i>Animal pharmacology (OVRD/DVP)</i>	Ching-Long Joseph Sun, PhD – June 3, 2019 Dmitriy Volokhov, DVM, PhD – December 18, 2019
Labeling Reviews • <i>APLB (OCBQ/APLB)</i>	Oluchi Elekwachi, PharmD, MPH • PNR Memo – November 28, 2018 • Labeling review – November 4, 2019
Other Reviews • <i>Metagenomics Analysis (OVRD/DVP)</i> • <i>Analytical methods and product testing (OCBQ/DBSQC)</i>	Arifa Khan, PhD – December 18, 2019 Marie Anderson, MS, PhD – November 13, 2019 Consolidated Memo from DBSQC: Anil Choudhary, PhD, MBA – December 13, 2019 Simleen Kaur, PhD – December 13, 2019 Ritu Agarwal, PhD – December 13, 2019

1. Introduction

Merck Sharp & Dohme Corp. (MSD) submitted Biologics License Application (BLA) 125690 for licensure of Ebola Zaire Vaccine, Live. The proprietary name of the vaccine is ERVEBO. ERVEBO is a vaccine indicated for the prevention of disease caused by *Zaire ebolavirus* (ZEBOV) in individuals 18 years of age and older. The vaccine is administered as a single intramuscular dose.

ERVEBO is a live, attenuated vaccine consisting of a recombinant vesicular stomatitis virus (VSV) backbone in which the VSV envelope glycoprotein has been deleted and substituted with the envelope glycoprotein of the ZEBOV (Kikwit 1995 strain). The vaccine virus is grown in serum-free Vero cell cultures. The virus is harvested from the cell culture (b) (4), and purified via (b) (4) steps prior to formulation with stabilizer solution. The bulk drug substance is stored in (b) (4) at (b) (4). To manufacture the final

drug product, the bulk drug substance is (b) (4) mixed with a (b) (4) stabilizer solution, filled into vials and stored frozen at $-70\pm 10^{\circ}\text{C}$.

ERVEBO is supplied in a carton containing ten single-dose vials. Each 1 mL dose is formulated to contain ≥ 72 million plaque forming units (PFU) of vaccine virus in the stabilizer solution consisting of 10 mM Tromethamine (Tris) and 2.5 mg/mL rice-derived recombinant human serum albumin. The dating period for the final drug product is 36 months from the date of manufacture when stored at $-70\pm 10^{\circ}\text{C}$.

2. Background

Ebola virus disease (EVD) is a rare but severe, zoonotic, highly contagious and often deadly disease affecting humans and nonhuman primates. EVD is caused by infection with one of four species of *Ebolavirus* (*Zaire*, *Sudan*, *Tai Forest*, *Bundibugyo*) belonging to the family *Filoviridae*, genus *Ebolavirus*, with the *Zaire ebolavirus* species recognized as the most virulent. Ebola virus was first discovered in 1976 near the Ebola River in what is now the Democratic Republic of the Congo.¹ Sporadic outbreaks of EVD have been observed in Africa, including 20 known outbreaks between 1976 and 2014,² with case fatality rates ranging from 25% to 90%.³ A recent outbreak in Guinea, Liberia and Sierra Leone resulted in 28,616 cases and 11,310 deaths between 2014-2016.⁴ In an ongoing outbreak of Ebola in the Democratic Republic of the Congo, over 3,300 cases and more than 2,200 deaths have been reported since the outbreak was declared on August 1, 2018.⁵

Zoonotic transmission of the virus from wild animals (such as fruit bats, porcupines and nonhuman primates) to humans leading to epidemics. Human-to-human transmission occurs through contact with the blood, secretions, organs or other bodily fluids of a person who is sick with or has died from EVD or via contact with surfaces and materials contaminated with infected bodily fluids.

The incubation period for Ebola virus is between 2 to 21 days, with an average of about 8 to 10 days. In the early stage of disease, symptoms of EVD can appear abruptly and include fever, severe headache, muscle pain, fatigue, weakness, and sore throat. EVD can progress to include vomiting, diarrhea, and massive fluid losses, including those related to external and/or internal hemorrhagic events (a condition known as Ebola hemorrhagic fever), in some cases precipitating hypotension and organ failure (i.e., shock), and death. Survivors of EVD may experience long term sequelae, including arthralgia, ocular complications, anorexia, or a number of neurologic complications, such as hearing loss, difficulty sleeping, and difficulty swallowing.^{6,7,8}

The persistence of Ebola virus in immunologically privileged sites⁹ has been reported in EVD survivors. Following resolution of infection, Ebola virus RNA has been detected in semen, breastmilk, aqueous humor, and cerebrospinal fluid of these survivors. Sexual transmission of EVD from a survivor to a previously uninfected partner has been reported.¹⁰

There is no vaccine, drug, or biologic approved in the US for the prevention or treatment of EVD, although several investigational vaccines, monoclonal antibodies, and antivirals are in clinical development. The European Commission granted a Conditional Marketing Authorization for ERVEBO on November 11, 2019, and the WHO prequalified ERVEBO on November 12, 2019.

Treatment of EVD consists of supportive care, such as rehydration with oral and/or intravenous fluids with electrolytes, maintaining adequate oxygenation, managing fever and pain, as well as treating secondary bacterial infections and other complications.

ERVEBO was developed at the Public Health Agency of Canada, and commercial rights were licensed to NewLink Genetics Corp., Ames, Iowa. In November 2014, Merck entered into a license agreement with NewLink Genetics to further develop, manufacture and distribute ERVEBO. Over the course of the development of ERVEBO, CBER held several consultations with Merck. The following agreements were reached regarding the content and timing of the submission of the BLA:

- January 30, 2017: CBER agreed that the Traditional Approval pathway for licensure based on efficacy data from the Guinea Ring Vaccination Study (V920-010) was an acceptable approach, provided that the BLA includes additional supportive safety and immunogenicity data. CBER recommended that the primary efficacy analysis be based on the endpoints that were pre-specified in the clinical study protocol and final statistical analysis plan.
- October 11, 2018: CBER agreed to Merck's proposal for a rolling BLA submission, starting in October 2018, with the submission of nonclinical data, and ending with the submission of the Drug Substance Process Performance Qualification (PPQ) results which would start the PDUFA review clock. In addition, CBER agreed that data for Drug Product PPQ Lot (b) (4) could be submitted during the review cycle, and that data from Drug Product PPQ Lots (b) (4) could be submitted post-licensure.
- November 11, 2018: In order to facilitate an expedited review of the BLA, CBER agreed to revise the October 11, 2018 agreement, such that the review clock would start upon the submission of the interim report for (b) (4) Drug Substance PPQ lots.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

Product Composition:

ERVEBO is a suspension for intramuscular (IM) injection manufactured by aseptic addition of the Bulk Drug Substance (BDS) to a stabilizer solution which consists of 2.5 g/L rice-derived recombinant human serum albumin, 10 mM Tris, (b) (4), and Water for Injection. Each 1 mL dose may contain residual amounts of host cell DNA (≤ 10 ng) and benzonase (≤ 15 ng). The vaccine may contain a trace amount of rice protein. The product contains no preservative. The composition of the ERVEBO Drug Product (DP) per 1 mL dose is provided in Table 1.

Table 1: Composition of the ERVEBO Drug Product

Component	Quantity (per 1 mL dose)	Function
Recombinant <i>Zaire ebolavirus</i> Kikwit-95 envelope glycoprotein modified vesicular stomatitis virus	$\geq 7.2 \times 10^7$ PFU	Active Ingredient
Tromethamine (Tris)	0.01 mmol	Buffer
Human serum albumin, recombinant rice-derived	2.5 mg	Stabilizer

Component	Quantity (per 1 mL dose)	Function
Water for Injection	Quantity Sufficient	Solvent

PFU: plaque forming unit

Manufacturing Process Development:

The ERVEBO manufacturing process was developed at the contract manufacturing facility, (b) (4), at a (b) (4) scale per Drug Substance (DS) lot. The (b) (4) scale manufacturing process was (b) (4) to the (b) (4) scale at the MSD pilot plant in (b) (4). The applicant provided a retrospective analysis of BDS lots manufactured at (b) (4) compared to DS lots made at the MSD (b) (4) site. The analysis indicated similar trends in (b) (4) and demonstrated the feasibility of process (b) (4). In consultation during product development, CBER agreed that the analysis demonstrated comparability between the DS lots manufactured at (b) (4) and MSD (b) (4).

The DP lots used in the clinical studies in the ERVEBO clinical development program were manufactured at (b) (4), except for the three DP lots used in the clinical lot consistency study (V920-012), which were produced at the MSD (b) (4) pilot plant from DS manufactured at the (b) (4) scale at (b) (4).

ERVEBO will be commercially manufactured at the MSD (b) (4) at the (b) (4) scale. In a consultation with Merck during product development, CBER agreed that Merck did not need to repeat the clinical consistency study using DP lots produced at the (b) (4) facility if Merck demonstrated that the DS PPQ lots produced at the (b) (4) facility are analytically comparable to the (b) (4) lots used to manufacture DP for the clinical studies. Merck met this condition and submitted data for (b) (4) DS PPQ lots produced at the MSD (b) (4) facility to the BLA. Using prespecified methods and acceptance criteria for (b) (4), the applicant demonstrated that the (b) (4) process at (b) (4) was analytically comparable to the (b) (4) process at (b) (4).

ERVEBO Drug Substance:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

ERVEBO Drug Product:

The manufacturing process for the ERVEBO DP consists of the following steps:

- The DP Stabilizer Solution consisting of rice-derived recombinant human serum albumin and Tris buffer is (b) (4) into a formulation vessel.
- The BDS is (b) (4) added to the vessel to achieve the formulation target of (b) (4). The (b) (4) is adjusted to (b) (4), and the mixture is stirred to ensure homogeneity of the (b) (4). The DP batch size range is (b) (4) for the (b) (4). The (b) (4) may be held at (b) (4) for up to (b) (4) prior to filling.
- The (b) (4) DP is filled into (b) (4) 2 mL glass vials, stoppered, capped and then inspected, labeled and packaged prior to freezing and storage at -70±10°C.

Specifications and Methods

The tests and specifications applied for routine release of the ERVEBO DP are shown in Table 2 below.

Table 2: Control of the Drug Product: Release Specifications

Test Parameter	Analytical Procedure	Acceptance Criteria
Sterility	(b) (4)	No growth
Bacterial Endotoxins	(b) (4) method (b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)
Identity	(b) (4)	Confirm rVSVΔG-ZEBOV-GP*
Physical Assessment – Color	Visual inspection (b) (4)	(b) (4)
Physical Assessment – Opalescence	Visual inspection (b) (4)	(b) (4)
Physical Assessment – Particulates	Visual inspection (b) (4)	No visible particulates

Test Parameter	Analytical Procedure	Acceptance Criteria
(b) (4)	(b) (4)	(b) (4)
Extractable Volume	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Total Protein	(b) (4) assay	(b) (4)

*rVSVΔG-ZEBOV is another name for the ERVEBO vaccine virus; GP: glycoprotein

(b) (4)
(b) (4)

Analytical Methods

The analytical methods and their validations and/or qualifications reviewed for the ERVEBO (b) (4) DP were found to be adequate for their intended use, except for the following test methods: Total Protein and (b) (4) Tests. Merck has provided written agreement to complete the validation of these test methods post-licensure.

Potency

Potency is measured by a (b) (4) assay in (b) (4). The initial (b) (4) assay was performed on the DP lots used in the clinical development program by (b) (4). The assay was later slightly modified and validated at (b) (4). (b) (4) clinical materials were re-analyzed using the new (b) (4) potency assay. The results obtained differed slightly; the potency as determined by (b) (4) for the dose used in the Phase 2/3 clinical studies ((b) (4)) was reassigned a potency value of 7.2×10^7 PFU/mL. The specification for stability studies and the label claim were set to this value. The commercial potency specifications for the DP were calculated to account for losses over the product shelf life and to reflect the highest dose tested in the clinic. The DP potency release specification was set to (b) (4).

Stability

The proposed expiry period for the ERVEBO DP manufactured at MSD (b) (4), is 36 months from the date of manufacture when stored at $-70 \pm 10^\circ\text{C}$. The date of manufacture is defined as the date of manufacture of the (b) (4). Stability data for the DP manufactured at MSD (b) (4) will be available post-licensure; therefore, the applicant provided supplemental information on the stability testing data for (b) (4) DP lots manufactured at (b) (4) and (b) (4) DP lots manufactured at Merck (b) (4). The methods used to evaluate the stability of the DP batches were selected with the intent of ensuring the quality of the vaccine with respect to container closure integrity, potency and general quality characteristics. The methods used include: Appearance, (b) (4), Potency, Bacterial Endotoxin, Container Closure Integrity (CCI), and Sterility. The stability data generated from these lots supports the 36-month expiry period for ERVEBO DP stored at $-70 \pm 10^\circ\text{C}$.

Container Closure System

The ERVEBO drug product is filled into (b) (4), 2 mL clear borosilicate glass vial ((b) (4)) with a 13 mm (b) (4) gray, (b) (4) stopper ((b) (4)) and 13 mm aluminum crimp seal with dark red plastic flip-off cap ((b) (4)). The container closure integrity testing was verified using the (b) (4) at (b) (4) located in (b) (4); all acceptance criteria were met.

Adventitious Agents Testing

Merck provided data to demonstrate the absence of extraneous agents in the (b) (4) used during manufacture of ERVEBO. In addition, in-process testing demonstrated that no extraneous agents were introduced during the manufacturing process. No materials of human or animal origin are used for the DS manufacturing and for the formulation of the DP. Viral (b) (4) studies using (b) (4) were performed to expand the risk assessment for potential contaminating viruses. No extraneous viruses were detected in these studies.

CMC Issues Resolved During the Review

Merck agreed to submit the following CMC information post-licensure as supplements to the BLA:

- Final stability results for the ongoing studies of the (b) (4) DP PPQ lots
- Assessment of (b) (4) on future DS lots
- Results of a one-time supplemental verification for the (b) (4) test using a (b) (4)
- Updated operating targets and ranges for the manufacturing process
- Data to support the total processing time for the final DP process

b) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

c) Facilities Review/Inspection

Facilities information and data provided in the BLA were reviewed by CBER. The facilities involved in the manufacture of Ebola Zaire Vaccine, Live are listed in Table 3 below. In addition, the activities performed, and inspectional histories are noted in the table.

Table 3: Manufacturing Facilities Table for Ebola Zaire Vaccine, Live

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Results/ Justification
Drug Substance and Drug Product Manufacturing MSD (b) (4) (b) (4) (b) (4)	(b) (4)	(b) (4)	Pre-License Inspection	CBER (b) (4) VAI
Drug Product Release Testing (b) (4) (b) (4) (b) (4)	(b) (4)	(b) (4)	Waiver	Team Bio (b) (4) VAI
Drug Product Release Testing and Stability Testing (b) (4) (b) (4) (b) (4)	(b) (4)	(b) (4)	Waiver	Team Bio (b) (4) NAI

VAI: Voluntary Action Indicated; **NAI:** No Action Indicated

CBER conducted a pre-license inspection (PLI) of the MSD (b) (4) facility from (b) (4), for DS and DP manufacturing. At the end of the inspection, CBER issued a Form FDA 483. The firm responded to the observations, and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

d) Environmental Assessment

The applicant submitted an environmental assessment in accordance with 21 CFR 25.15(a) that evaluated potential environmental impacts due to the use and disposal of ERVEBO. Vaccine virus RNA has been detected in saliva, urine, and fluid from skin vesicles in adults. The primary concern with shedding of live virus vaccines is transmission to potentially susceptible individuals. Transmission of ERVEBO to livestock is also a theoretical possibility. Based on data provided in the environmental assessment report, as well as clinical data demonstrating limited shedding of the vaccine virus in adults, the results of the biodistribution and persistence study in nonhuman primates (NHPs), and the lack of horizontal transmission of the vaccine virus in

swine, its potential environmental impact is considered negligible. The environmental assessment provided by the applicant is adequate.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

General Toxicology

ERVEBO was evaluated in a repeat dose toxicity study in cynomolgus macaques. Two intramuscular vaccine administrations on Study Days 1 and 14 at doses up to 1×10^8 PFU (as determined by the (b) (4) potency assay) were well-tolerated. Expected local and immunogenic responses to vaccine administrations were observed and not considered to be adverse. There was no evidence of vaccine related systemic or local toxicity.

Developmental and Reproductive Toxicity Studies

An exploratory immunogenicity and viremia study in rats demonstrated a sustained and robust immune response and a transient viremia (after the first dose of vaccine), which supported the use of the rat model for the developmental and reproductive toxicology study. In the developmental toxicity study, female rats were administered a single human dose of ERVEBO by intramuscular injection on four occasions: 28 days and 7 days prior to mating, gestation Day 6 and lactation Day 7. No adverse effects on pre-weaning development up to post-natal Day 21 were observed. There were no vaccine-related fetal malformations or variations observed.

Nonclinical Pharmacology Supporting Vaccine Effectiveness

ERVEBO has been shown to be protective in challenge models in multiple species, including mice, hamsters, guinea pigs and NHPs. Immunogenicity and effectiveness of ERVEBO was evaluated in three NHP studies. In the first study, cynomolgus macaques were given a single IM dose of 3×10^6 , 2×10^7 or 1×10^8 PFU (as determined by the (b) (4) potency assay). Monkeys were challenged by the IM route 42 days post-vaccination with 1000 PFU of ZEBOV Kikwit strain. All vaccinated animals developed vaccine-specific IgG ELISA and neutralizing antibody titers, starting at 14 days post-vaccination and peaking at 28 to 36 days post-vaccination. All animals challenged in the two higher dose groups survived challenge; seven of eight animals survived challenge in the lowest dose group. In a second study, lower doses of ERVEBO were evaluated, ranging from 3×10^6 PFU down to 3×10^2 PFU (as determined by the (b) (4) potency assay). All vaccinated animals survived challenge with 1000 PFU of ZEBOV at Day 42 post-vaccination and mounted similar immune responses as observed in the first study.

Additional Nonclinical Studies

A biodistribution study in cynomolgus macaques was performed to assess for vaccine virus RNA by qRT-PCR and the presence of live vaccine virus by plaque assay. Persistence of vaccine virus RNA was observed primarily in lymphoid tissues throughout the study (112 days). Plaque assay detected replication-competent virus only on Day 1 post-vaccination. The presence of viral RNA after Day 7 was generally confined to tissues that lack potential for shedding in excretions or secretions, and no distribution was observed in the brain or spinal cord at any time point. In addition, the absence of neurovirulence was demonstrated in cynomolgus macaques following intrathalamic brain inoculation with a developmental lot of ERVEBO.¹¹

To support the environmental risk assessment, the ability of ERVEBO to replicate in arthropod cell cultures of relevant vector species and in relevant vector species was evaluated. No replication was detected. The infectivity and potential for transmission of ERVEBO in swine was also assessed, which demonstrated a lack of horizontal transmission of the vaccine virus in swine in this experimental setting.

5. CLINICAL PHARMACOLOGY

Immunization with ERVEBO results in an immune response and protection from disease caused by *Zaire ebolavirus*. The relative contributions of innate, humoral and cell-mediated immunity to protection from *Zaire ebolavirus* are unknown.

6. CLINICAL/STATISTICAL

a) Clinical Program

Overview

The clinical development program for ERVEBO included clinical studies conducted in North America, Europe and Africa. A total of 15,997 adult subjects were vaccinated with ERVEBO or a lower dose formulation in these studies; 15,399 of these subjects received a dose of $\geq 7.2 \times 10^7$ PFU (as determined by the (b) (4) potency assay), which is the licensed dose of ERVEBO. This SBRA will focus on the study that provided data on the effectiveness of ERVEBO (V920-010), the study that provided lot-to-lot consistency immunogenicity and safety data (V920-012), as well as the studies that provided safety and supportive immunogenicity data (V920-009, V920-011).

Summary of Clinical Vaccine Effectiveness

The effectiveness of ERVEBO was established in a single efficacy study (V920-010) conducted during the 2014-2016 Ebola outbreak in the Republic of Guinea. V920-010 was a Phase 3 open-label, cluster-randomized study comparing immediate versus delayed vaccination against EVD. Index cases (persons newly diagnosed with EVD) were identified by the Guinean national surveillance system. A cluster (or ring) definition team defined the cluster population by creating a list of all contacts and contacts of contacts (CCC), relative to the index case, regardless of eligibility for vaccination, including absent CCCs. From the complete cluster list, preliminary inclusion and exclusion criteria were applied to generate a list of all potential trial participants (eligible CCCs) to be approached for consent. Once the cluster list was finalized and closed, eligible CCCs were cluster-randomized to immediate or delayed vaccination (21 days later). Allocation of a cluster to either immediate or delayed vaccination was done once the enumeration of the cluster (i.e., the list of CCCs) was complete. A separate consent team obtained written informed consent from all eligible CCCs. Eligible CCCs cluster-randomized to immediate vaccination had only one opportunity to give their informed consent (Day 0), while eligible CCCs assigned to the delayed clusters had an opportunity to consent on Day 0 and/or Day 21. Subjects were informed of the cluster allocation at the end of the informed consent process.

The primary, prespecified efficacy outcome was confirmed EVD, defined as: 1) any probable or suspected case from which a blood sample taken was laboratory-confirmed as positive for EVD; or 2) any deceased individual with probable EVD from which a post-mortem sample taken within 48 hours after death was laboratory-confirmed as positive for EVD. The analysis period for

assessing efficacy and the populations selected for the primary efficacy analysis were not prespecified. In amendments to the Statistical Analysis Plan, the analysis period was defined as events that occur between D and 21+D days. The per protocol primary analysis value for D was not fixed and defaulted to the intent-to-treat analysis where D=10. Based on regulatory feedback, the study population for the primary efficacy analysis included only those subjects in the delayed vaccination group who consented at Day 0 to control for comparison group bias by addressing efficacy among prospectively consenting individuals.

Initial treatment groups included adult subjects randomized to receive either immediate or delayed vaccination with ERVEBO. Due to an interim analysis demonstrating 100% vaccine efficacy and the waning Ebola outbreak in Guinea, the Data Safety Monitoring Board recommended discontinuation of randomization procedures, immediate vaccination for all identified rings, and inclusion of children 6-18 years of age. The protocol was also amended to expand vaccination to areas of Sierra Leone adjoining the border of Guinea.

A total of 476 confirmed cases of EVD were identified as index cases. Of the 361 excluded cases, the majority (n=273; 76%) were excluded due to distance, delayed reporting, or inadequate team capacity. Rings were defined for the remaining 115 cases and for 2 additional cases from Sierra Leone (non-randomized), for a total of 117 rings comprising a total population of 11,841 CCCs. Ninety-eight rings (9,096 subjects) were randomized: 51 rings (4,539 subjects) were randomized into immediate vaccination clusters, and 47 rings (4,557 subjects) were randomized into delayed vaccination clusters. Among 19 non-randomized rings (2,745 subjects), 3 were pilot rings and 16 were discontinued based on the recommendation of the DSMB. Among 4,539 subjects in immediate vaccination clusters, 2,119 (47%) were eligible, consented (at Day 0), and vaccinated. Among 4,557 subjects in delayed vaccination clusters, 1,435 (31%) were eligible and consented (at Day 0), and an additional 1,104 subjects (24%) were consented at Day 21.

The primary efficacy analysis (all vaccinated subjects in the immediate group versus all subjects who were eligible and consented at Day 0 in the delayed group) included 3,537 subjects $\geq$ 18 years of age. Of these, 2,108 were included in 51 immediate vaccination clusters, and 1,429 were included in 46 delayed vaccination clusters. Cases of EVD that occurred between Days 10 and 31 post-randomization of the cluster were included in the analysis. Cases of EVD reported between the reference start time and Day 10 were censored to maintain the comparability of the populations with respect to exposure to the index case. Cases occurring after Day 31 were also censored to account for vaccination on Day 21 in the delayed group. No cases of confirmed EVD were observed in the immediate group, and a total of 10 confirmed EVD cases were observed in 4 rings in the delayed group, resulting in a point estimate of vaccine efficacy (VE) of 100% (95% CI: 63.5% to 100%). There were no EVD cases after 32 days post-randomization. Additional efficacy analyses, some of which were not prespecified, were conducted to assess potential sources of bias and were generally comparable to the primary analysis.

Lot Consistency

V920-012 was a Phase 3 randomized, double-blind, placebo-controlled study to evaluate the safety and immunogenicity of (b) (4) consistency lots and a high dose lot of ERVEBO in healthy adult subjects 19 to 65 years of age at study sites located in the US, Canada, and Spain. Subjects were randomized 2:2:2:2:1 to receive either a single dose of one of (b) (4) consistency lots of ERVEBO (7.2×10^7 PFU/dose, as determined by the (b) (4) potency assay), a High Dose lot of ERVEBO ((b) (4)), as determined by the (b) (4) potency assay) or saline placebo. Among 1,197 randomized subjects, 1,061 received ERVEBO. The primary objective of

this study was to demonstrate consistency in the immune responses of subjects who received one of the three consistency lots at 28 days post-vaccination. The primary endpoint was the geometric mean titer (GMT) at Day 28 post-vaccination for antibody titers as measured by anti-ZEBOV-GP enzyme-linked immunosorbent assay (ELISA) in all subjects. For the primary statistical analysis, the pre-specified criterion to demonstrate consistency required the 2-sided 95% confidence interval (CI) on the pairwise lot-to-lot comparison of the anti-ZEBOV-GP-ELISA GMT ratio to be between 0.5 and 2.0 (primary objective) or 0.67 and 1.50 (secondary objective).

The pair-wise ratios of GP ELISA GMTs at Day 28 post-vaccination for subjects who received one of three ERVEBO are shown in Table 4 below.

Table 4: GP-ELISA GMT Ratios at Day 28 Post-vaccination

DP lots compared	N	GMT ratio (95% CI)
Lot A: Lot B	239: 231	0.94 (0.77, 1.14)
Lot A: Lot C	239: 226	0.88 (0.71, 1.09)
Lot B: Lot C	231: 226	0.94 (0.77, 1.15)

Source: Adapted from STN 125690/0 Clinical Study Report for V920-012

N: Number of subjects in the Per-Protocol immunogenicity analysis

GMT: Geometric Mean Titer

The primary objective of lot-to-lot consistency in terms of anti-ZEBOV-GP specific ELISA GMTs at Day 28 post-vaccination was met, as the two-sided 95% CI of GMT ratios between all three pairs of lots were within the pre-specified criterion of 0.5 and 2.0; the secondary objective was also met, as the two-sided 95% CI of GMT ratios between all three pairs of lots were within 0.67 and 1.50.

Clinical Immunogenicity

Three studies assessed antibody responses to ERVEBO (Study V920-009, Study V920-011, and Study V920-012). Study V920-012 has been described above.

V920-009, named Partnership for Research on Ebola Vaccines in Liberia (PREVAIL), was a Phase 2/3 randomized, double-blind, placebo-controlled trial which evaluated the safety and immunogenicity of Ebola vaccine candidates, including ERVEBO, in healthy, adult subjects. In this study, subjects were randomized 1:1 to receive ERVEBO or saline placebo. A total of 500 subjects were vaccinated with ERVEBO and assessed for immunogenicity.

V920-011, named Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE), was a Phase 2/3 randomized open-label study which evaluated the safety and immunogenicity of ERVEBO in adults ≥ 18 years of age or older working in healthcare facilities or on frontline activities related to the Ebola response in Sierra Leone. In this study, 8,673 adult subjects were randomized 1:1 to immediate (within 7 days of enrollment) or deferred (18 to 24 weeks after enrollment) vaccination with ERVEBO. A total of 7,998 subjects were vaccinated with ERVEBO, with a subset of subjects (n=508) assessed for immunogenicity.

Tests for antibody responses included the detection of ZEBOV (Kikwit) GP-specific immunoglobulin G (IgG) by ELISA and the assessment of neutralization of vaccine virus by a plaque reduction neutralization test (PRNT). Antibody responses among subjects in the study conducted in the US, Canada and Spain were similar to the responses among subjects in the studies conducted in Liberia and Sierra Leone. A measure of the immune response that confers protection against EVD is unknown.

Bioresearch Monitoring

No Bioresearch Monitoring (BIMO) inspections were performed for this BLA.

b) Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Merck requested a partial waiver of studies of ERVEBO in children 0 through 11 months of age because studies are impossible or highly impracticable (Section 505B(a)(5)(B)(i) of the Act).

Merck requested a partial deferral of studies in children 12 months through 16 years of age because ERVEBO is ready for approval for use in adults before pediatric studies are complete (Section 505B(a)(4)(A)(i)(I) of the Act).

Merck's pediatric study plan was presented to FDA's Pediatric Review Committee on October 8, 2019. The committee agreed with the applicant's request for a partial waiver of studies in children 0 through 11 months of age and a partial deferral of studies in children 12 months through 16 years of age.

The study required by PREA specified in the approval letter for this application, and agreed upon with Merck, is the deferred study V920-016 to evaluate the safety and immunogenicity of ERVEBO in children 12 months through 17 years of age. The applicant will submit the final study report as a supplement to the BLA by June 30, 2021.

7. SAFETY/PHARMACOVIGILANCE

Safety

The safety profile of ERVEBO has been assessed in 8 Phase 1 studies (including 5 blinded and placebo-controlled studies and 3 open-label studies), and 4 Phase 2/3 studies (including 2 blinded and placebo-controlled studies and 2 open-label studies). The Phase 2/3 studies V920-009 and V920-012 (see Section 6 for overview) contributed most of the safety data; additional details regarding collection of safety data for these studies are described below.

Study V920-009, conducted in Liberia, enrolled 1,000 subjects who were randomized 1:1 to receive ERVEBO or saline placebo. Evaluation for solicited local and systemic reactions was performed at Week 1 and Month 1 post-vaccination. In a subset of subjects (n=201), joint symptoms and signs were also solicited during a Week 2 visit. Memory aids were not used, and post-vaccination temperatures were measured only at study visits. Unsolicited adverse events were collected through Month 1 post-vaccination. A total of 56.4% of subjects reported at least one of the solicited systemic adverse reactions listed in Table 5 within seven days after vaccination. Except for one subject who reported an event of moderate intensity, all others reported mild intensity events.

Table 5: Percentage of Subjects with Solicited Local and Systemic Adverse Reactions After Vaccination for study V920-009

--	ERVEBO (%)	PLACEBO (%)
Injection-site reactions*	N= 500	N= 500
Injection site pain	34.0	11.2
Local reactions (redness/swelling)	1.8	0.8
Systemic adverse reactions†	N= 498	N= 499
Headache	36.9	23.2
Feverishness	34.3	14.8
Muscle pain	32.5	22.8
Fatigue	18.5	13.4
Nausea	8.0	4.4
Joint pain/tenderness	7.0	5.8
Rash	3.6	3.2
Abnormal sweating	3.2	2.6
Arthropathy (Joint redness/warmth)‡	0.6	0.2
Joint swelling‡	0.4	0.4
Joint stiffness‡	0.4	0.2

* Adverse reactions were solicited at 30 minutes, Week 1 and Month 1 postvaccination.

† Adverse reactions were solicited at Week 1 and Month 1 postvaccination.

‡ In a subset of subjects (n=201), joint symptoms and signs were also solicited during a Week 2 visit.

Study V920-012, conducted in the United States, Canada and Spain, enrolled 1,197 subjects who were randomized 4:1 to receive ERVEBO or saline placebo. Subjects used a memory aid to record solicited local reactions from Days 1 to 5 post-vaccination, and daily temperature measurements and solicited joint and skin events from Days 1 to 42 post-vaccination. The only systemic adverse events solicited for V920-012 were for joint, skin and mucosal events, as described below in Table 6. Unsolicited adverse reactions were collected through Day 42 post-vaccination.

Table 6: Percentage of Subjects with Solicited Local and Systemic Adverse Reactions After Vaccination for Study V920-012

--	ERVEBO (%)	Placebo (%)
Injection-site reactions*	N= 1051	N= 133
Injection-site pain	69.5	12.8
Injection-site swelling	16.5	3.0
Injection-site redness	11.9	1.5
Systemic adverse reactions†	N= 1051	N= 133
Joint pain	17.9	3.0
Arthritis (composite term)‡	4.7	0.0
Rash (composite term)§	3.8	1.5
Vesicular lesions¶	1.5	0.0

*Adverse reactions were solicited Days 1 to 5 postvaccination.

†Adverse reactions were solicited Day 1 through Day 42 postvaccination.

‡Arthritis is a composite term that includes preferred terms of arthritis, monoarthritis, polyarthritis, osteoarthritis, joint swelling, or joint effusion.

§Rash is a composite term that includes petechiae, purpura, rash, rash generalized, rash macular, rash papular and rash vesicular.

¶Vesicular lesions include events reported as rash vesicular in the rash composite term and reported as blister.

Additional observations identified from evaluation of the totality of the safety data that were considered potentially clinically important are described below.

Unsolicited Adverse Reactions

In Study V920-012 (described above), the unsolicited adverse reaction of chills was reported in 7.3% of ERVEBO recipients compared to 0% of placebo recipients. Paresthesia was reported by 1.4% of ERVEBO recipients compared to 0% of those who received placebo in this study.

Arthralgia and arthritis

Arthralgia was reported to occur in 7% to 40% of vaccine recipients in blinded, placebo-controlled studies. Arthralgia was generally reported in the first few days following vaccination, was of mild to moderate intensity and resolved within one week after onset. Severe arthralgia, defined as preventing daily activity, was reported in up to 3% of subjects.

Arthritis (arthritis, joint effusion, joint swelling, osteoarthritis, monoarthritis or polyarthritis) was reported to occur in 0% to 24% of subjects in blinded, placebo-controlled studies in which subjects received ERVEBO or a lower dose formulation, with all but one study reporting arthritis in < 5% of subjects. Most occurrences of arthritis were reported within the first few weeks following vaccination, were of mild to moderate intensity, and resolved within several weeks after onset. In a Phase 1 study conducted in Geneva, Switzerland (V920-005), 24 out of 102 subjects (24%) who received ERVEBO or a lower dose formulation reported events of arthritis, compared to none of the 13 placebo recipients, with some cases reported as severe and prolonged (up to 2 years post-vaccination). In some tested subjects with arthritis, vaccine virus RNA was detected in the synovial fluid by RT-PCR. These findings were not replicated in the Phase 2/3 studies (see Tables 5 and 6).

Rash

Across the two blinded studies that provided the most data for skin and mucosal lesions (V920-009 and V920-012), the proportions of subjects reporting solicited skin-related events were generally comparable between the ERVEBO (3.6% to 3.8%) and placebo (1.5% to 3.2%) groups, although vesicular lesions were observed only after ERVEBO in V920-012. In one Phase 1 Study (V920-005), rash was reported to occur in 25% of ERVEBO recipients and 7.7% of placebo recipients. In this study, cutaneous vasculitis was reported in two subjects who received a lower dose formulation, neither of whom had evidence of systemic vasculitis. Vesicular fluid and skin biopsy samples taken from some subjects reporting rash have tested positive for vaccine virus RNA by RT-PCR.

Decreases in Lymphocytes and Neutrophils

White blood cell counts were assessed in 697 subjects who received ERVEBO. Decreases in lymphocytes were reported in up to 85% of subjects and decreases in neutrophils were reported in up to 43% of subjects. No associated infections were reported.

Severe Adverse Events

Among 15,399 ERVEBO recipients, two serious adverse reactions of pyrexia and two serious adverse reactions of anaphylaxis were reported as vaccine-related. There were no other imbalances in SAEs (including fatal SAEs), or patterns that were considered clinically meaningful, or appeared mechanistically or temporally linked to ERVEBO administration.

Pharmacovigilance

Merck submitted a proposed Risk Management Plan (RMP) that included a Pharmacovigilance Plan (PVP) for ERVEBO intended to address “Identified Risks,” “Important Potential Risks” and “Missing Information” (RMP, Version 1.0, dated February 26, 2019). There are no identified risks. The potential risk of “viral shedding/secondary transmission to close contacts, particularly immunocompromised hosts” is adequately addressed with routine pharmacovigilance. Missing information on “exposure during pregnancy,” “exposure during lactation,” and “exposure in HIV-infected individuals” will be collected in ongoing studies.

Merck submitted a revised RMP (Version 2.0, dated August 23, 2019) to remove “safety and reduced efficacy in immunocompromised hosts” as a potential risk in the PVP. Although CBER recommended that the PVP include both “arthritis” and “safety and reduced efficacy in immunocompromised hosts” as potential risks, Merck indicated that no additional pharmacovigilance activities are planned to further characterize these potential risks. CBER found Merck’s rationale for not including “arthritis” and “safety and reduced efficacy in immunocompromised hosts” in the PVP to be acceptable, as data regarding these potential risks will be available for analysis through routine pharmacovigilance. The proposed pharmacovigilance plan for ERVEBO included in the RMP, version 2.0, dated August 23, 2019, is adequate for the labeled indication.

8. ADVISORY COMMITTEE MEETING

This submission was not discussed at a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting because FDA review of this submission did not identify concerns or issues which would have benefited from an advisory committee discussion.

9. OTHER RELEVANT REGULATORY ISSUES

None.

10. LABELING

The proposed proprietary name, ERVEBO, was reviewed by the Advertising and Promotional Labeling Branch on November 28, 2018. CBER communicated the acceptability of the proprietary name to the Applicant on January 18, 2019. The Advertising and Promotional Labeling Branch reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and Package and Container labeling on November 4, 2019, from a promotional and comprehension perspective.

The review team negotiated revisions to the PI, including the modification of the proposed proper name from “Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP, Live, Attenuated)” to “Ebola Zaire Vaccine, Live.” Merck proposed the following indication: “ERVEBO is a vaccine indicated for active immunization of at-risk individuals 18 years of age and older to protect against Ebola Virus Disease (EVD) caused by Zaire Ebola Virus.” The indication was revised to “ERVEBO is a vaccine indicated for the prevention of disease caused by *Zaire ebolavirus* in individuals 18 years of age and older” for global harmonization of the labeling for this product.

Two statements were added to the Limitations of Use section to indicate that the duration of protection conferred by ERVEBO is unknown, and that ERVEBO does not protect against other species of *Ebolavirus* or *Marburgvirus*. The Warnings and Precautions section was revised to

include the following: (1) a statement to advise ERVEBO participants to continue to adhere to infection control practices to prevent EVD infection and transmission; (2) a statement that indicates that anaphylaxis has been observed following administration of ERVEBO, and that appropriate medical treatment and supervision must be available in case of anaphylactic event following the administration of ERVEBO; and (3) a statement that indicates that vaccine virus RNA has been detected in plasma, saliva, urine and fluid from skin vesicles after vaccination, and that transmission of vaccine virus is a theoretical possibility.

All labeling issues regarding the PI and the carton and container labels were resolved following the exchange of information and discussions with the applicant.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

Based on the review of the clinical, nonclinical, and product-related data submitted in the original BLA, the Review Committee recommends approval of ERVEBO for the labeled indication and usage.

b) Risk/ Benefit Assessment

The applicant has submitted data to the BLA to support the safety and efficacy of ERVEBO. Considering the high morbidity and mortality associated with EVD, the Review Committee agrees that the risk/benefit balance for ERVEBO is favorable and supports approval for use in individuals 18 years of age and older.

c) Recommendation for Postmarketing Activities

Merck has committed to conduct the following postmarketing activities which are specified in the approval letter for this application:

PEDIATRIC REQUIREMENT

1. Deferred study V920-016 to evaluate the safety and immunogenicity of ERVEBO in children 12 months through 17 years of age.

Final Protocol Submission: October 21, 2016

Study Completion Date: January 31, 2020

Final Report Submission: June 30, 2021

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

2. To provide the Final Drug Product process performance qualification final validation report as a "Postmarketing Commitment – Final Study Report."

Final Report Submission: May 29, 2020

12. REFERENCES

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