



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Epidemiology (DE)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

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To: Stephanie Polo
Chair of the Review Committee

Through: Manette Niu MD
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Director, DE
OBE, CBER, FDA

Subject: Pharmacovigilance Plan Review

Sponsor: Merck

Product: ERVEBO, Ebola Zaire Vaccine, Live

Application Type/Number: BLA/ STN 125690

Approved Indication: The prevention of disease caused by Zaire ebolavirus in individuals 18 years of age and older.

Submission Date: 9/13/2019

Action Due Date: 3/16/2020

1 Objective

The purpose of this review is to assess the adequacy of the pharmacovigilance plan (PVP) based on the safety profile of ERVEBO.

2 Product Information

2.1 Product description

ERVEBO is a live recombinant viral vaccine consisting of a vesicular stomatitis virus (VSV) backbone deleted for the VSV envelope glycoprotein and substituted with the envelope glycoprotein of the Zaire ebolavirus (Kikwit 1995 strain). The vaccine is manufactured in serum-free Vero cell cultures. Each 1 mL dose of ERVEBO contains a minimum of 72 million plaque forming units (pfu) of virus vaccine in a stabilizer solution containing 10 mM Tromethamine (Tris) and 2.5 mg/mL rice-derived recombinant human serum albumin.

2.2 Proposed dosing regimen(s) and formulation(s)

Administration of a single 1 mL dose of ERVEBO intramuscularly.

3 Materials Reviewed

Table 1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
10/31/2018	Merck	BLA Sequence 0000	Modules: 2.7.4, Summary of clinical safety 1.16, Risk management plans
9/5/2019	Merck	BLA Sequence 0031	1.16, Risk management plans
10/9/2019	Merck	BLA Sequence 0038	Module 1.11.3 Clinical Information Amendment Response to Information Request from CBER Dated 26-Sep-2019
12/2/2019	Merck	BLA Sequence 0050	Module 1.14.1.3 Draft PI
12/4/2019	Merck	BLA Sequence 0052	Module 1.11.3 Clinical Information Amendment Response to Information Request from CBER Dated 25-Nov-2019

4 Summary of Prior Marketed Experience

Not applicable. Product does not have a history of regulatory approval and general use outside the US.

The vaccine is currently being administered as part of the outbreak response in the Democratic Republic of Congo (DRC) through compassionate use.

5 Brief description of Safety Database

The safety database included data from 12 clinical studies, 8 Phase 1 and 4 Phase 2/3 trials, and included 15,399 ERVEBO vaccine recipients, who are included in the safety pool. The preponderance of data is from three clinical studies conducted during the epidemic in West Africa. The PREVAIL study (V920-009) in Liberia was a randomized controlled trial (RCT) with 500 subjects in each of the vaccination and placebo arms. The Guinea study (V920-010), was a randomized ring vaccination trial consisting of an immediate (n=2119), and delayed (n=2041) vaccination group. The STRIVE study in Sierra Leone (V920-011) was a randomized open-label trial with an immediate vaccination group (n=4165), and a deferred vaccination group (n=3833, and referred to as the deferred crossover group after vaccination) of individuals vaccinated between 18 to 24 weeks post-enrollment. In addition, V920-012 was an RCT conducted in the US, Canada, and Spain to study safety and immunogenicity, and consisted of subjects (n=1061) randomized to 4 different lots with different amounts of plaque-forming units (pfu) or placebo (n=133). Three different lots had 2×10^7 and one had 1×10^8 pfu.

The studies assessed the prophylactic efficacy, safety, and immunogenicity of ERVEBO when administered to individuals over 18 years of age, and generally excluded children, HIV positive individuals, and pregnant women. However, there were 234 children 6-18 years of age, 278 pregnancies, and 22 HIV positive-individuals who received ERVEBO in the clinical trials.

Each clinical trial determined the safety data they would collect, and there is no prespecified plan to harmonize data across studies for analysis. The type and duration of data collection varied across studies; Table 2 from the clinical summary of safety describes the data collected by each trial. The longest duration of follow-up was 2 years.

Table 2 from page 25-26 of Summary of Clinical Safety: Types of Adverse Events and Collection Time Points in the V920 Clinical Trials

Trial Number	Trial Design and Blinding Status	Country	Subject Memory Aid Use (Yes or No)	CSR MedDRA Version	AE Category				
					Solicited Injection-Site and Systemic Adverse Events	Unsolicited Adverse Events	Serious Adverse Events	Viremia and Viral Shedding	Clinical Laboratory Safety Tests
V920-001	Randomized, double-blind	United States	Yes	17.0	Day 1 to 14	Day 1 to 28	Day 1 to 180	Day 0, 1, 3, 7, 14	Day 0, 1, 3, 7, 28, 180
V920-002	Randomized, double-blind	United States	Yes	17.0	Day 1 to 14	Day 1 to 28	Day 1 to 365	Day 0, 3, 7 following each dose	Day 0, 7, 28, 35, 56 following each dose
V920-003	Randomized, double-blind	Canada	Yes	17.0	Day 1 to 14	Day 1 to 28	Day 1 to 180	Day 0, 1, 3, 7, 14	Day 0, 1, 3, 7, 28, 180
V920-004	Randomized, double-blind	United States	Yes	17.0	Cohort 1: Day 1 to 14	Cohort 1: Day 1 to 28	Day 1 to 360	Day 0, 1, 2, 3, 4, 7, 14, 28	Day 0, 7, 28
V920-005	Randomized, double-blind	Switzerland	Yes	17.0	Day 1 to 14	Day 1 to 28	Day 1 to 365	Day 0, 1, 3, 7	Day 0, 1, 3, 7, 14, 28, 365(only blood count at Day 365)

V920-006	Open-label	Germany	Yes	17.0	Day 1 to 14	Day 1 to 28	Day 1 to 180	Day 0, 1 to 7, 14, 28	Day 0, 1, 3, 7, 14, 28, 180
V920-007	Open-label	Gabon	Yes	17.0	Day 1 to 14	Day 1 to 28	Day 1 to 365	Day 0, 1, 2 and	Day 0, 1, 2, 7, 28, 84, 180, 365
V920-008	Open-label	Kenya	Yes	17.0	Day 1 to 14	Day 1 to 28	Day 1 to 365	Day 0, 1, 3, 7	Day 0, 7, 30
V920-009	Randomized, double-blind	Liberia	No	20.0	Week 1, Week 2, Month 1	Week 1 and Month 1	Week 1, Month 1 And 2, every 2 months to trial end	Not collected	At Week 1 and Month 1
V920-010	Randomized ring vaccination, open-label	Guinea	No	Not applicable	Minute 30, Day 3 and Day 14	Day 1 to 14	Day 1 to 84	Not collected	Not collected
V920-011	Randomized, open-label	Sierra Leone	Yes	19.0	Safety Sub-Study subjects: Day 0 to 28	Overall Population: Day 0 to 28	Overall Population: Day 0 to 180	Not collected	Not collected
V920-012	Randomized, double-blind	United States, Canada, Spain	Yes	19.1	Day 1 to 42	Day 1 to 42*	Day 1 to Month 24	Not collected	As needed for arthralgia, arthritis, rash or vesicles follow-up only

6 Sponsor's Pharmacovigilance Plan

Table 3: Pharmacovigilance Plan from Sponsor Risk Management Plan – version 0.2 (page 27-28, BLA sequence 31)

Safety concern	Benefit risk impact
Important identified risks	
None	Not applicable
Important potential risks	

Viral shedding/secondary transmission to close contacts, particularly immunocompromised hosts	<p>Vaccine viremia was commonly observed among rVSVΔG-ZEBOV-GP recipients in the trials in which vaccine viremia was assessed. Viremia generally resolved in adult cases by 14 days postvaccination. Viral shedding (identification of rVSVΔG-ZEBOV-GP virus in saliva and urine) was also observed in a few adult subjects.</p> <p>Preliminary data from the V920-007 trial demonstrated that viral RNA shedding was more frequent in children and adolescents compared with adults. Additional trials are ongoing which will further evaluate viral shedding.</p> <p>Although transmission of the virus through contact is a theoretical possibility, it is considered low risk because of the low magnitude of shedding. Transmission of vaccine virus was not evaluated in clinical trials with rVSVΔG-ZEBOV-GP.</p>
Missing information	
Exposure during pregnancy	Pregnant and breastfeeding women were excluded from rVSVΔG-ZEBOV-GP trials; however, a number of women were incidentally found to be pregnant after vaccination. As a precautionary measure, it is preferable to avoid the use of rVSVΔG-ZEBOV-GP during pregnancy and pregnancy should be avoided for 2 months following vaccination. The vaccine should be administered during pregnancy only if clearly needed.
Exposure during lactation	Data for subjects who were breastfeeding in the V920 clinical trials are not available. It is unknown whether rVSVΔG-ZEBOV-GP is secreted in human milk. Vaccine-virus-associated risks in infants breastfed by mothers vaccinated with rVSVΔG-ZEBOV-GP are unknown.

Safety concern	Benefit risk impact
Exposure in HIV-infected individuals	<p>Twenty-two subjects with known HIV infection received rVSVΔG-ZEBOV-GP (Study V920-009). Although no differences in safety profile were observed in these subjects compared with healthy adults receiving the vaccine, their immunologic status (CD4 count) was not known and the small sample size limits the safety conclusions that can be drawn. Additional trials are underway to further characterize the safety profile of rVSVΔG-ZEBOV-GP in HIV-infected subjects.</p>

7 Analysis of Sponsor's Pharmacovigilance Plan

7.1 Important potential risk: Viral shedding/secondary transmission to close contacts, particularly immunocompromised hosts

The Sponsor identified viral shedding in the saliva and urine of vaccinated adults in Phase 1 trials. The rate was less than 10% in the larger Phase 1 studies, and no virus was detected in saliva beyond day 6.

In addition, studies identified vesicular rash as an Adverse Event (AE) associated with vaccination. In the Phase 1 trials, V920-005, 8.8% (n=9) subjects developed vesicular rash; RT-PCR identified vaccine virus in five subjects, one of whom had detectable virus in skin lesions until day 28. In the Phase 2/3 trial, rates of vesicular lesions occurred in 1.5% of vaccinated subjects. The Sponsor did not provide information on the identification of vaccine virus in these subjects.

The Sponsor reported no transmission of vaccine virus to unvaccinated individuals.

Reviewer comment: Viral shedding is a well-recognized potential risk associated with the administration of live virus vaccines. The ERVEBO clinical trials demonstrate the potential for viral shedding and transmission at a low rate during a relatively short post-vaccination time period. No cases of transmission to vaccinee contacts were reported, however, viral shedding and the potential for viral transmission to contacts remains a theoretical risk, so inclusion in the PVP as a potential risk is acceptable.

7.2 Important potential risk: Safety and reduced efficacy in immunocompromised hosts

The original PVP submitted with this BLA identified “safety and reduced efficacy in immunocompromised hosts” as a potential risk, which was addressed by routine pharmacovigilance. The Sponsor's updated PVP (received by CBER September 5, 2019) notes that they incorporated the EMA's request to remove “safety and reduced efficacy in immunocompromised hosts” as a potential risk, and instead addressed this risk through labeling.

Of note, the development program for ERVEBO excludes immunocompromised individuals, including HIV-positive individuals or those with AIDS, which are classified as a separate risk group.

Reviewer comment: DE, in an Information Request (IR, 11/25/2019), conveyed to the Sponsor the difference in objectives between the PVP (to identify important risks to ensure that data are adequately collected for evaluation during post-marketing surveillance) and product labeling (to inform providers and patients about product issues, e.g. risk, efficacy and safety). DE requested that the Sponsor amend the PVP so that the “safety and reduced efficacy in immunocompromised hosts” remains a potential risk.

The Sponsor (Clinical Information Amendment, 12/4/2019) did not accept DE's request, stating that the safety concern in immunocompromised hosts is covered through labeling (Warning and

Precautions section), and it is not necessary to identify this separately in the PVP since it will be assessed by routine pharmacovigilance.

DE notes that the purpose of the PVP is to identify important risks that warrant consideration, and ensure that data on such issue is collected and evaluated as part of postmarketing surveillance in routine regulatory documents (i.e., Periodic Safety Update Report [PSUR]). It is useful to specify that immunocompromised hosts are an identified risk in the PVP, as live virus vaccines pose a potential safety concern to this population.

DE will analyze relevant postmarketing data for this issue, which should still be available through routine pharmacovigilance.

7.3 Important identified/potential risk: Arthritis

The Sponsor identified arthritis as an AE initially in Phase 1 trials, and results from Phase 2/3 studies continued to show this association with ERVEBO vaccination. Table 4 shows a comparison between the rate of arthritis in ERVEBO compared to placebo recipients, and is suggestive of an increased rate of arthritis in vaccine recipients. Additionally, two trials (V920-005, and V920-012), identified vaccine virus in the synovial fluid of individuals with symptomatic arthritis (100% (n=3/3) and 33% (n=1/3), respectively).

Table 4: Comparison of the Number and Percentage of Arthritis Cases in ERVEBO Vaccine Trials in Patients Who Received Vaccine vs Placebo

Clinical Trial	Vaccine arm	Placebo arm
V920-004 – US phase 1	4.5% (19/418)	3.2% (3/94)
V920-005 – Switzerland phase 1	23.5% (24/102) [3/3 synovial fluid tests positive for virus]	0% (0/13)
V920-009 – Liberia PREVAIL, RCT	1.2% (7/500)	0.8% (4/500)
V920-010 – Guinea randomized ring vaccination	0% (0/4160)	Not Applicable (study population either immediately vaccinated, or had delayed vaccination)
V920-011- Sierra Leone STRIVE, safety substudy	2.9% (6/225)	0.9% deferred vaccination (2/224)

Clinical Trial	Vaccine arm	Placebo arm
V920-011 - Sierra Leone STRIVE, overall	0.2% Immediate (9/4165) 0.1% Deferred crossover (3/3821)	Not Applicable
V920-012 – US, Canada, Spain, RCT	3.7% Combined Lots (29/791) 3.1% High Dose (8/260) [1/3 synovial fluid tests positive for virus]	0% (0/133)

Of note, there was a shorter median time to onset of arthritis in vaccinated subjects vs. placebo (8 to 11 days for vaccinated subjects vs. 34.5 to 47 days for placebo).

Except for the larger Phase 2 and 3 studies conducted during the West African epidemics (009, 0010, 0011), a marked increase in arthritis events was reported in ERVEBO recipients when compared to placebo.

Reviewer comment: Identification of arthritis as an AE following ERVEBO administration in the Phase 1 trials, the potential significance of vaccine virus identified in the synovial fluid of symptomatic subjects, and the shorter median time to onset of symptoms in vaccinees compared to controls suggests a possible association between arthritis and ERVEBO. The lower reported rate of arthritis in the larger Phase 2/3 trials conducted during an international emergency epidemic response in low income countries may be the result of limited follow-up. Thus, the extent of potential pathology from this AE in the general population remains unknown.

DE sent an IR (dated 11/25/2019) to the Sponsor requesting the addition of arthritis as either an identified or potential risk to the PVP, which could be addressed with routine pharmacovigilance.

The Sponsor (Clinical Information Amendment, 12/4/2019) did not accept this request, and stated that AEs should be included in the PVP only if it changes the risk-benefit calculation.

DE recommends that an AE should be included in a PVP if it is deemed important enough to warrant regular monitoring and analysis in regulatory documents, or if the AE needs to be better characterized.

DE agrees that in the context of ring vaccination during an epidemic response, it is unlikely that even rare severe events or sequelae due to a vaccine-induced arthritic reaction could change the risk-benefit assessment, since Ebola infection is frequently fatal. The vaccine, however, may be used more broadly; should a Ministry of Health (MOH) decide to administer ERVEBO as part of

a mass vaccination campaign, or a potential healthcare responder choose to deploy and get vaccinated, the risk-benefit balance could change.

Arthritis is an AE included in the manufacturer's package insert (Adverse Reactions Section). DE will analyze relevant postmarketing data for this issue, which should still be available through routine pharmacovigilance.

7.4 Missing information: Exposure during pregnancy, Exposure during lactation

The Sponsor identified exposure during pregnancy and lactation to ERVEBO vaccine as missing information, since pregnant and lactating women were excluded from trials submitted to the BLA.

The Sponsor reported data from pregnant women inadvertently exposed to ERVEBO. A total of 278 pregnancies were reported from clinical trials submitted by the sponsor. Exact exposure time relative to conception or the Last Menstrual Period (LMP) was not reported, but 107 women were reported as pregnant within 2 months after vaccination. The sponsor's assessment of the available data did not reveal specific safety concerns. Sixty percent (n=58/97) of pregnancies, not lost to follow-up, resulted in live births; no congenital anomalies were reported.

The Sponsor cited a WHO-sponsored trial: "Compassionate ring vaccination study to evaluate the safety of the Ebola vaccine in the Democratic Republic of the Congo (DRC)," but this data was not submitted as part of this BLA.

Reviewer comment: Studies collected information on pregnant and lactating women inadvertently exposed to ERVEBO. The available data did not specify the exact time of exposure and did not suggest a specific safety concern. The data, while limited, was collected in low income countries with limited health systems, where births may not occur in a healthcare facility or with a skilled birth attendant.

DE requested (IR dated 9/26/2019) that the Sponsor utilize a pregnancy questionnaire to follow-up reports of pregnancy exposure, report data to the agency in a systematic manner by utilizing the table in Appendix A, and provide a case series analysis of serious AEs associated with pregnancy (e.g. congenital anomaly, fetal death, etc.). The Sponsor agreed to this request.

CBER is planning to request the final study reports from the WHO-sponsored studies in DRC be submitted to the BLA for review when they are available.

7.5 Missing information: Exposure in HIV-infected individuals

Most studies submitted to this BLA excluded HIV-positive individuals. Trial V920-009 (PREVAIL Liberia) enrolled 22 HIV-positive subjects in the vaccination arm, and 31 HIV-positive individuals in the placebo group. Although the HIV-positive study population is small, when compared to HIV-negative vaccinees, the AE profile was similar, with subjects reporting malaria as the most frequent serious AE.

The sponsor cited an ongoing trial (V920-015) that they are not conducting and was not submitted to this BLA: “A Phase 2 Randomized, Multi-Center Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Immunogenicity of the V920 (rVSVΔG-ZEBOV-GP) Ebola Virus Vaccine Candidate in HIV-Infected Adults and Adolescents.”

Reviewer comment: Information on HIV-positive subjects exposed to ERVEBO does not suggest a safety concern, but is limited, thus, this remains as missing information.

CBER is planning to request the final study reports for V920-015 be submitted for review to the BLA when available.

8 Additional considerations: Pediatric populations

Under the Pediatric Research Equity Act (PREA), CBER is requesting the sponsor complete a post-marketing requirement (PMR): “Deferred study V920-016 to evaluate the safety and immunogenicity of ERVEBO in children 1 through 17 years of age,” as pediatric populations were not generally studied in the trials submitted to this BLA.

9 Conclusions

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, for which CBER will request the final study reports.

CBER requests the sponsor complete a PREA pediatric PMR as part of approval.

There were several potential risks (arthritis, safety and reduced efficacy in immunocompromised hosts) that DE requested the Sponsor include in the PVP that the Sponsor declined to incorporate. DE recognizes the public health benefit of rapid approval of this vaccine, and that data regarding these potential risks will be available for analysis through routine pharmacovigilance. The Sponsor’s PVP is acceptable.

10 Recommendations

Table 3: Summary of PVP

	Important Safety Concern	Pharmacovigilance Action
	Important identified safety concerns	
1	None identified	<ul style="list-style-type: none"> No actions
	Important potential safety concerns	

	Important Safety Concern	Pharmacovigilance Action
2	Viral shedding/secondary transmission to close contacts, particularly immunocompromised hosts	<ul style="list-style-type: none"> Routine pharmacovigilance as required under 21 CFR 600.80
Important missing information		
3	Exposure during pregnancy	<ul style="list-style-type: none"> Ongoing study, CBER to request final study report: “Compassionate ring vaccination study to evaluate the safety of the Ebola vaccine in the Democratic Republic of the Congo” Utilization of follow-up questionnaire Systematic reporting of pregnancy data from routine pharmacovigilance activities
	Exposure during lactation	<ul style="list-style-type: none"> Ongoing study, CBER to request final study report: “Compassionate ring vaccination study to evaluate the safety of the Ebola vaccine in the Democratic Republic of the Congo”
	Exposure in HIV-infected individuals	<ul style="list-style-type: none"> Ongoing study, CBER to request final study report: “A Phase 2 Randomized, Multi-Center Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Immunogenicity of the V920 (rVSVΔG-ZEBOV-GP) Ebola Virus Vaccine Candidate in HIV-Infected Adults and Adolescents”

CBER is also requesting the Sponsor complete a PREA pediatric PMR as part of approval.

No additional actions recommended prior to approval. The Sponsor’s proposed PVP is adequate.

Please see the final version of the Package Insert (PI) submitted by the Sponsor for the final agreed-upon language describing ERVEBO.

Appendix A: Table: Number of cases of pregnancy and fetal outcomes in pregnancies with exposure to Ebola vaccine

	Spontaneous Postmarketing Reports (n=X)												Clinical Trials (reported pre- and postmarketing) (n=X)						Other - please specify sources (n=X)					
Time of Report	Prospective (n=X) Time of Exposure						Retrospective (n=X) Time of Exposure																	
Outcome	Total DPO	PTL	1st Tri	2nd Tri	3rd Tri	Unk	Total DPO	PTL	1st Tri	2nd Tri	3rd Tri	Unk	Total DPO	PTL	1st Tri	2nd Tri	3rd Tri	Unk	Total DPO	PTL	1st Tri	2nd Tri	3rd Tri	Unk
Unknown outcome																								
Spontaneous abortion < 28 weeks w/o CA																								
Spontaneous abortion < 28 weeks with CA																								
Spontaneous abortion < 20 weeks w/o CA [†]																								
Spontaneous abortion < 20 weeks with CA [†]																								
Elective abortion w/o CA																								
Elective abortion of fetus w/ CA																								
Ectopic																								
Molar																								
Fetal death ≥ 28 weeks w/o CA																								
Fetal death ≥ 28 weeks with CA																								
Fetal death ≥ 20 weeks w/o CA [†]																								
Fetal death ≥ 20 weeks with CA [†]																								
Live births																								
Preterm LB (< 37 weeks)																								
LB w/ CA																								
LB with Major CA*																								

[illegible]

Total DPO = Total distinct pregnancy outcomes (total number of cases for the listed outcome with an exposure during pregnancy. If there are multiple exposures and gestations, so that the sum of the exposures in different time periods do not add up to the total DPO, please provide information to clarify)

PTL = prior to last menstrual period (up to 30 days before last menstrual period)

Tri = trimester

Unk = unknown time of exposure

LB = Live birth

CA = Congenital anomaly

* Please provide a definition for major and minor congenital anomalies.

ⁱPlease provide spontaneous abortion and fetal death numbers with a cutoff of 20 weeks if this data is available. The data with cutoff points of 20 weeks and 28 weeks should include data for the whole period described (so data for 28 weeks should not be additional cases between 20 and 28 weeks, but for the whole period before or after 28 weeks).