BLA Clinical Review Memorandum

Application Type	Efficacy Supplement
STN	125690/55
CBER Received Date	June 27, 2022
PDUFA Goal Date	April 27, 2023
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Omolara Adewuni, MD, MPH, MBA
Review Completion Date / Stamped Date	July 27, 2023
Supervisory Concurrence	Andrea Hulse, MD Branch Chief, CRB2
Applicant	Merck Sharp & Dohme Corp.
Established Name	Ebola Zaire Vaccine, Live
(Proposed) Trade Name	Ervebo
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	1 mL suspension for injection supplied as a single-dose vial
Dosage Form(s) and Route(s) of Administration	1 mL suspension for intramuscular injection
Dosing Regimen	Single dose
Indication(s) and Intended Population(s)	Indicated for the prevention of disease caused by *Zaire ebolavirus* in individuals 12 months of age and older
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
ANOVA	analysis of variance
APaT	All Participants as Treated
BLA	biologics license application
BMI	body mass index
CBER	Center for Biological Evaluation and Research
CI	confidence interval
CRF	case report form
CSR	clinical study report
CVD	Center for Vaccine Development
DRC	Democratic Republic of Congo
DSMB	data safety monitoring board
eCRF	electronic case report form
EBOV	Ebola virus
ELISA	enzyme-linked immunosorbent assay
EVD	Ebola virus disease
FAS	full analysis set
GMFI	geometric mean fold increase
GMT	geometric mean titer
GP-EBOV	Ebola virus glycoprotein
GP-ELISA	glycoprotein enzyme-linked immunosorbent assay
ICF	informed consent form
iPSP	initial pediatric study plan
IR	information request
PeRC	Pediatric Review Committee
PFU	plaque-forming unit
PI	Prescribing Information
PP	per-protocol
PREA	Pediatric Research Equity Act
PRNT	plaque reduction neutralization test
RMP	risk management plan
rVSV	recombinant vesicular stomatitis virus
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental biologics license application
SCD	sickle cell disease
ZEBOV	*Zaire ebolavirus*

1. EXECUTIVE SUMMARY

Ebola virus disease (EVD), formerly known as Ebola hemorrhagic fever, is a rare but severe, often fatal illness that spreads via human-to-human contact (WHO, 2021). Since identification of the virus in 1976 in the Democratic Republic of the Congo, the largest outbreaks have occurred in the West African countries of Guinea, Liberia, and Sierra Leone, causing approximately 28,000 cases and 11,000 deaths between 2013 and 2016 (ECDC, 2022). Of the six known species of *ebolavirus*, *Zaire ebolavirus* has the highest mortality rate (60%-90%) with some of the highest mortality rates in young children.

Ebola Zaire Vaccine, Live (trade name Ervebo) was approved in December 2019 for active immunization for the prevention of disease caused by *Zaire ebolavirus* in individuals 18 years of age and older. The efficacy of Ervebo was established in adults in a single efficacy study (V920-010) conducted during the 2014-2016 Ebola outbreak in Guinea. Pediatric assessment as required by the Pediatric Research Equity Act (PREA) was deferred at the time of the original biologics license application (BLA) approval because the product was ready for use in adults and pediatric studies had not been completed.

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc (the Applicant) submitted a supplemental BLA (sBLA) containing results from Study V920-016 (also known as Partnership for Research on Ebola VACcination or PREVAC): a Phase 2, randomized, double-blind, placebo-controlled study evaluating the safety and immunogenicity of Ervebo in individuals 12 months of age and older. The study evaluated three vaccine strategies: Ad26.ZEBOV/MVA-BN-Filo vaccine (Janssen), and V920 (Ervebo by Merck) with or without a second booster dose at Day 56This submission fulfills the Applicant's postmarketing requirement (PMR) to evaluate the safety and effectiveness of Ervebo in a pediatric population.

The content of the sBLA and the scope of this review are limited to the assessment of the data supporting a single, 7.2×10^7 plaque-forming units (PFU), dose of Ervebo compared to a single placebo dose in individuals 12 months of age and older. A total of 2002 participants (998, 12 months to 17 years of age; 1004, 18 years and older) were randomized 1:1 to Ervebo or placebo.

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The primary immunogenicity objective was to demonstrate that Ervebo was noninferior for antibody response 28 days postvaccination in pediatric participants (12 months through 17 years of age) as compared to adult participants (18 years of age and older). The primary immunogenicity endpoint was Ebola virus glycoprotein (GP-EBOV) antibody response at Day 28 post-randomization, as measured by glycoprotein enzyme-linked immunosorbent assay (GP-ELISA). The secondary Immunogenicity endpoints were:

- GP-EBOV antibody response at Month 3 and Month 12 post-randomization post first vaccination, as measured by GP-ELISA, and
- Neutralizing antibody response at Day 28, Month 3, and Month 12 post-randomization, post first vaccination, as measured by plaque reduction neutralization test (PRNT).

The immunogenicity success criterion was a lower bound (LB) of the 2-sided 95% confidence interval (CI) of the GMT ratio of the GP-EBOV antibody response in pediatric participants/adult participants at Day 28 as measured by GP-ELISA >0.5. Blood samples for immunogenicity testing were obtained at baseline (prior to vaccination) and at Day 28, Month 3, and Month 12 from all randomized participants. The primary immunogenicity endpoint was met with a GMT ratio of 1.42 with a 2-sided 95% CI of 1.24, 1.62, where the lower limit of the CI was above the prespecified non-inferiority margin of 0.5; thus demonstrating that the immune response in

pediatric participants is non-inferior to the immune response in adult participants. Based on the non-inferior immune response in the pediatric population compared to the adult population, for which vaccine effectiveness was established based on clinical endpoints in the prevention of disease caused by *Zaire ebolavirus*, vaccine effectiveness is established for the pediatric population.

Safety was assessed for all vaccinated participants from baseline through Month 12 postvaccination; however, memory aids were not used. All pediatric and adult participants were monitored for safety for 30 minutes immediately following vaccination and then had study visits on Days 7, 14 and 28 postvaccination for assessment of injection site reactions, targeted systemic symptoms and Grade 3 and 4 unsolicited adverse events (AEs). Body temperature was measured on Days 7, 14, 28 and Month 6; Serious adverse events (SAEs) and malaria events were captured at all study visits through Month 12. In addition to the aforementioned assessments and assessment periods, pediatric participants were contacted daily on Days 1 – 6 to measure body temperature and assess injection site reactions, targeted systemic symptoms and Grade 3 and 4 unsolicited AEs. Participants were not given thermometers and did not record daily temperatures outside of the scheduled visits; instead, participants were queried regarding subjective feverishness since their last visit. Feverishness was recorded as a targeted systemic reaction. Any temperatures measured on-site and recorded as elevated temperatures were reported on case reports forms as AEs of pyrexia.

The most commonly reported AEs in the pediatric population were solicited adverse reactions including headache (59%); injection site pain (52%); [subjective] feverishness (48%); myalgia (30%); somnolence, reduced activity, fatigue (28%); abdominal pain (21%); chills (14%); myalgia (12%); and vomiting (11%). Grade 3 and 4 unsolicited AEs and were reported in a total of 4 participants reporting 1 event each (Grade 4: unilateral blindness, Grade 3: insomnia, hypertension and toothache). No Grade 3 or Grade 4 unsolicited AE or SAEs were considered related to vaccine. No study participant withdrew from study treatment or the study due to an AE. No new safety signals were observed in the study population.

Non-inferior immune responses in pediatric as compared to adult participants and a safety profile that is similar to the known safety profile of the licensed product in adults, in the context of the high morbidity and mortality associated with EVD, resulted in a favorable risk-benefit evaluation in support of expanding the use of Ervebo for prevention of disease caused by *Zaire ebolavirus* to the pediatric population. The clinical reviewer recommends Ervebo for approval in individuals 12 months and older based on this favorable risk-benefit profile.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Overall, a total of 2002 participants (1004 adult and 998 pediatric) received the licensed dose (7.2×10^7 PFU) of Ervebo. The median age of participants in Study V920-016 was 18 years (range 1 to 76 years). Approximately 50% (n=998) of the participants were <18 years of age, and 54.6% (n=1094) were male. One percent (n=19) of the participants were HIV-positive, and all HIV-positive participants were ≥18 years of age.

The median age of the 1004 adult participants in Study V920-016 was 27 years (range: 18 to 76 years). Approximately 98.2% (n=986) of the participants were between the ages of 18 and 65 years. The mean height, weight, and body mass index (BMI) were higher in the adult population than in the overall study population. All other characteristics were generally comparable between the adult population and the overall study population.

Study Demographics in Pediatric Participants

Table 1 below summarizes the demographic subgroups of pediatric participants (12 months through 17 years of age) in Study V920-016.

Table 1. Demographic Characteristics of Pediatric Participants 12 Months Through 17 Years of Age, Study V920-016

Characteristic	Ervebo 1 Dose N=407 n (%)	Ervebo 2 Dose N=202 n (%)	Pooled Ervebo[a] N=609 n (%)	Pooled Placebo[b] N=389 n (%)	Total N=998 n (%)
Pediatric age group	--	--	--	--	--
12 mos to <3 yrs	56 (13.8)	39 (19.3)	95 (15.6)	60 (15.4)	155 (15.5)
3-11 yrs	213 (52.3)	97 (48.0)	310 (50.9)	205 (52.7)	515 (51.6)
12-17 yrs	138 (33.9)	66 (32.7)	204 (33.5)	124 (31.9)	328 (32.9)
Mean (yrs)	8.6	8.2	8.4	8.3	8.4
Median (yrs)	9.0	8.0	9.0	8.0	8.0
Range (yrs)	1 to 17	1 to 17	1 to 17	1 to 17	1 to 17
Sex	--	--	--	--	--
Male	222 (54.5)	117 (57.9)	339 (55.7)	207 (53.2)	546 (54.7)
Female	185 (45.5)	85 (42.1)	270 (44.3)	182 (46.8)	452 (45.3)
Baseline serostatus	--	--	--	--	--
Baseline ELISA <200 EU/mL)	263 (68.1)	129 (66.2)	392 (67.5)	130 (64.0)	522 (66.6)
Baseline ELISA ≥200 EU/mL	66 (17.1)	33 (16.9)	99 (17.0)	40 (19.7)	139 (17.7)
Missing	57 (14.8)	33 (16.9)	90 (15.0)	33 (16.3)	123 (15.7)

Source: STN 125690.55, Clinical Study Report, Table 10.6 and 14.1-11, page 119 and 241
Abbreviations: ELISA=enzyme-linked immunosorbent assay
[a] Pooled Ervebo = Ervebo 1 dose or 2 doses
[b] Pooled placebo = 0.5 and 1.0 mL placebo groups

Three pediatric age groups were analyzed in Study V920-016: 12 months to <3 years; 3 to 11 years; 12 to 17 years. More than half of pediatric participants (51.6%) were 3 to 11 years of age, 32.9% were 12 to 17 years of age and 15.5% were 12 months to <3 years of age. A majority of subjects were male (55.7%) and seronegative (<200 EU/mL) at baseline (67.5%).

Subgroup analyses of the primary immunogenicity endpoint by pediatric age group, sex and baseline serostatus were consistent with the result for the overall primary immunogenicity endpoint.

The adverse event (AE) profiles for the subgroups of pediatric participants were generally consistent with the overall population with the following exceptions:

- Injection site AEs in the Ervebo groups were reported less frequently in pediatric participants <3 years of age than in the overall pediatric population.
- The proportion of participants who experienced ≥1 AE were comparable for the Ervebo and placebo groups in participants <3 years of age, but higher among Ervebo recipients than placebo recipients in participants 3 to 11 years of age and 12 to 17 years of age.

The proportions of pediatric and adult participants who reported serious adverse events (SAEs) were low and comparable across age subgroups. No SAEs (fatal and non-fatal) were

considered related to vaccination. The numbers of participants who died during the study were similar between age and treatment groups (5 pediatric participants: 3 in the 1-dose Ervebo group, 2 in the placebo group; 4 adult participants: 3 in the 1 dose group, 1 in the placebo group) . No deaths were reported for pediatric participants younger than 3 years of age.

1.2 Patient Experience Data

Patient experience data was not submitted as part of this application.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Introduction

Zaire ebolavirus (ZEBOV) is a negative stranded RNA virus in the Filoviridae family. *Zaire* is one of three virus species in the *Ebolavirus* genus that cause human disease outbreaks in regions of Africa where Ebola is endemic. Zoonotic transmission of the virus from wild animals (such as fruit bats, porcupines, and non-human primates) to humans results in epidemics through human-to-human transmission via direct contact with the blood, secretions, organs or other bodily fluids of infected people or corpses and via contact with surfaces and materials contaminated with infected body fluids (WHO, 2023).

Epidemiology

Sporadic outbreaks of Ebola disease have been observed in Africa, including 20 known outbreaks between 1976 and 2014 (Malvy, 2019). The Ebola outbreak during 2014 to 2016 in West Africa (Guinea, Liberia, and Sierra Leone) was the largest since the virus was first discovered in 1976; it resulted in 28,616 cases of Ebola virus disease (EVD) and 11,310 deaths (CDC, 2019). The index case for this outbreak was reported in Guinea in December 2013 and an outbreak was declared on March 23, 2014, at which time 49 confirmed cases and 29 deaths were reported. The outbreak spread to the neighboring countries of Liberia and Sierra Leone. Cases were reported in an additional 7 countries. Liberia was declared Ebola-free January 14, 2016, followed by Sierra Leone on March 7, 2016, and Guinea in June 2016 (CDC, 2019).

Numerous *Zaire ebolavirus* outbreaks have occurred in West and Central Africa since the 2014 to 2016 outbreak, mainly in the Democratic Republic of Congo (DRC), resulting in over 3,770 reported cases and over 2,450 reported deaths as of December 19, 2021 (WHO, 2021). In 2021, three outbreaks in North Kivu Province, DRC (February and October 2021) and N'Zérékoré Prefecture, Guinea (February 2021) were presumed to be from persistent infections in EVD survivors, based on genetic sequencing that suggested the outbreaks were not caused by spillover from animal reservoirs (CDC, 2022).

Clinical Course and Sequelae

The incubation period of Ebola is between 2 to 21 days. Clinical manifestations of EVD include the abrupt onset of non-specific symptoms including fever, fatigue, muscle pain, headache, and sore throat in the early stage of disease. These symptoms are followed by vomiting and diarrhea which can result in massive fluid losses. Shock can follow, along with organ failure and external and internal hemorrhagic events. Laboratory findings include low white blood cell and platelet counts and elevated liver enzymes (Malvy, 2019; WHO, 2023). In previous outbreaks, the case fatality rate ranged from 25% to 90% (WHO, 2023); in the recent 2014-2016 outbreak, the total mortality was 11,325 deaths out of 28,652 cases, for a case-fatality rate of 39.5%. Among the countries with the highest transmission rates, the case-fatality rates were 28% in

Sierra Leone, 45% in Liberia, and 66.7% in Guinea (Shultz, 2016). Survivors of EVD may experience long-term sequelae, including arthralgia, ocular complications, anorexia, hearing loss, difficulty sleeping, and difficulty swallowing (Tiffany, 2016; Qureshi, 2015; Clark, 2015).

The persistence of EBOV in immunologically protected reservoirs has been reported in EVD survivors. Following resolution of infection, EBOV RNA has been detected in semen, breastmilk, aqueous humor, and cerebrospinal fluid. Sexual transmission of EBOV from a survivor to a previously uninfected partner provides evidence of the transmission potential from these immunologically protected sites (Dokubo, 2018).

During the EVD epidemic in West Africa (2014), approximately 20% of all cases were in children <16 years, and the mortality rate in those aged <5 years 89.5% (CI 95%: 75.9, 95.8) (WHO, 2015) underscoring the need for an effective vaccine in children.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently, there are two FDA-approved therapies for the treatment of *Zaire ebolavirus* infection in adult and pediatric patients. Each therapy is administered as a single intravenous infusion:

- Inmazeb, a combination of three *Zaire ebolavirus* glypcoprotein-directed human monoclonal antibodies (atoltivimab, maftivimab, and odesivimab-ebgn) approved October 14, 2020
- Ebanga, a single *Zaire ebolavirus* glypcoprotein-directed human monoclonal antibody (ansuvimab-zykl) approved December 21, 2020.

2.3 Safety and Efficacy of Pharmacologically Related Products

Ervebo is currently the only Ebola vaccine licensed and available for use in the US.

Ongoing clinical development programs are assessing the rVSVΔG vector, using inserts to elicit immune responses to other viral vectors. As of the time of this review, no major safety signals have been identified in these clinical development programs and no efficacy data are available.

Ongoing clinical development programs are assessing *Zaire ebolavirus* GP inserts in other viral vectors. As of the time of this review, no major safety signals have been identified in these clinical development programs.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Ervebo administered as a single dose for the prevention of *Zaire ebolavirus* disease in adults 18 years and older was approved in the European Union on November 11, 2019, and in the US on December 19, 2019. The efficacy of Ervebo was established in adults in a single efficacy study (V920-010) conducted during the 2014-2016 Ebola outbreak in Guinea. Please refer to Dr. Rebecca Reindel's clinical review of the original BLA submission for details. Following the EU and US approvals, Great Britain, Switzerland and nine African countries to date have approved Ervebo for use in adults for the prevention of disease caused by *Zaire ebolavirus*.

The Applicant reported that as of August 2022, 18,006 participants have received the marketed formulation and dose of Ervebo in Phase 1, 2, and 3 clinical studies. Injection site AEs were common, mostly mild to moderate in intensity. Pain was the most commonly reported injection

site AE in the Ervebo group. Arthralgia (joint pain) was reported in 5% to 50% of participants, and arthritis (joint swelling) less commonly reported (<5% in most studies and up to 24% in one study). The majority of joint pain events were mild to moderate in intensity and resolved in days (arthralgia) to weeks (arthritis). However, a few participants reported arthritis of prolonged duration, recurrence, and/or sequelae up to 2 years postvaccination.

In non-trial settings, approximately 4,800 individuals have been vaccinated with the marketed formulation and dose of Ervebo. The Applicant reported a total of 16 spontaneous safety reports (63 events: 1 serious, 62 nonserious) through January 31, 2022. The reported SAE was hypoxia but had limited additional information, which precluded a meaningful causality assessment. Headache was the most commonly reported nonserious event (10/62 events), followed by pyrexia (9/62 events), asthenia, myalgia (6/62 events each), injection site pain (5/62 events), arthralgia (3/62 events), diarrhea, nausea, chills (2/62 events each) and leukopenia, neutropenia, vomiting, adverse drug reaction, chest pain, fatigue, ill-defined disorder, malaise, injection site reaction, aspartate aminotransferase, dizziness, muscle contractions involuntary, tremor, dyspnea, hyperhidrosis, rash and hypotension (1 event each). The 16 safety reports were in 7 females, 8 males and 1 gender not reported. Patient age was reported in 14 cases and ranged from 28 to 46 years. No new safety signals were identified in the postmarketing safety data.

2.5 Summary of Pre- and Post-Submission Regulatory Activity Related to the Submission

- August 20, 2014: Initial IND 16131 submission
- May 13, 2016: Agreed initial pediatric study plan (iPSP), including a plan to request a partial waiver of the pediatric assessment for the population 0 through 11 months of age, and a plan to defer the assessment of the population 12 months through 17 years of age
- December 19, 2019: Approval of the original BLA for Ervebo in adults. The approval letter included Post Marketing Requirement (PMR) #1 to evaluate the safety and immunogenicity of Ervebo in pediatric participants 12 months through 17 years of age.
- March 21, 2022: Supplemental BLA (sBLA) to submit correlate of protection data from Study V920-018 and to update the Prescribing Information (PI) as indicated (STN 125690.51).
- June 27, 2022: sBLA submission of Study V920-016, to fulfill PMR #1 (STN 125690.55).
- September 29, 2022: sBLA (STN 125690.51) approved and PI revised with subjects from study V920-018. Correlate of protection (COP) data was not included in the PI due to the inability to define a threshold value for protection.
- February 28, 2023: Ervebo pediatric assessment presented to the Pediatric Review Committee (PeRC). CBER considers PMR #1 fulfilled with approval of the sBLA.

2.6 Other Relevant Background Information

Not applicable

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The sBLA was well organized, with all sections accessible and organized appropriately. CBER issued and received responses to several information requests (IRs) as detailed in Section 5.2.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The Applicant stated that Study V920-016 was conducted in a manner commensurate with the principles of Good Clinical Practice including Independent Ethics Committee review, informed consent, and the protection of individuals participating in biomedical research.

3.3 Financial Disclosures

The Applicant provided a signed Form FDA 3454 with a list of 26 investigators and sub-investigators for Study V920-016, and certified that they had not entered into any financial agreements with the investigators that could potentially influence the outcome of the study. The Applicant certified that each of the 26 listed investigators and sub-investigators disclosed their financial interests and that one of the investigators (Dr. Samba O. Sow) reported disclosable financial interests or arrangements as defined in 21 CFR 54.2.

Dr. Samba O. Sow (clinical study report [CSR] site # 0006 in Bamako, Mali) enrolled 228 participants and reported a significant payment of "other sorts" (b) (4), (b) (6) . A grant of (b) (4), (b) (6) was listed on the disclosure form. The Grant – entitled *Surveillance Study to Monitor Effectiveness and Safety of the Vaccine Vial Monitor (VVM) Compatible Formulation of RotaTeq™ in Routine Use in a Developing World Setting* – EP 08011.027 was awarded to Karen Kotloff at the Center for Vaccine Development (CVD), University of Maryland School of Medicine. Dr. Samba O. Sow (investigator) was included as a sub-contractor for CVD-Mali from October 2014 to March 2018 as reported by the investigator on 08-02-2017. Of note, this grant was related to *RotaTeq*™ and not Ervebo.

Reviewer Comment: *The payment of "other sorts"* (b) (4), (b) (6) *reported by Dr. Sow was not related to Dr. Sow's participation in PREVAC nor was it directly paid to him, but instead to the center where he was listed as a sub-contractor for a different study. Dr. Sow's participation as a sub-contractor in this unrelated study is unlikely to influence the outcome of PREVAC.*

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

4.1 Chemistry, Manufacturing, and Controls

No new information was submitted. Refer to Dr. Dmitry Volokhov's chemistry, manufacturing, and controls review in the original BLA for further details.

4.2 Assay Validation

No new information was submitted.

4.3 Nonclinical Pharmacology/Toxicology

No new nonclinical toxicology studies were required or conducted to support pediatric use. The safety of Ervebo in adults and the existing nonclinical data were sufficient to support evaluation in the pediatric population.

4.4 Clinical Pharmacology

No clinical pharmacology studies with Ervebo were conducted.

4.5 Statistical

The statistical reviewer verified the immunogenicity results in Study V920-016. Please see Dr. Ahnn Sang's biostatistical review for further details.

4.6 Pharmacovigilance

The risk management plan (RMP) was updated to support the supplemental marketing application requesting approval for the use of Ervebo in individuals 12 months through 17 years of age. There are no new or reclassified safety concerns.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The Applicant submitted the results of the Partnership for Research on Ebola VACcination (PREVAC) study, also called Study V920-016, in support of the sBLA. PREVAC is a randomized, double-blind, placebo-controlled, Phase 2 clinical study to evaluate the immunogenicity and safety of two Ebola vaccine candidates (Ervebo and Ad26.ZEBOV/MVA-BN-Filo) simultaneously. However, the intent of the sBLA is to provide immunogenicity and safety data to support extending Ervebo's indication for use to the pediatric population 12 months of age and older. Therefore, this submission does not include data relevant to the safety and effectiveness of the Ad26.ZEBOV/MVA-BN-Filo vaccines and any discussion of those vaccines will be limited in scope (e.g., V920-016 study design).

The original protocol for PREVAC was amended four times. No study participants were enrolled under versions 1.0 and 2.0. A total of 1034 participants were enrolled under version 3.0; however, those participants received half doses of Ervebo and are not included in the Applicant's or FDA's analyses supporting labeling changes associated with this sBLA. This review focuses on the 2802 participants who received the currently licensed dose of Ervebo (n=2002) or placebo (n=800) and were enrolled under version 4.0.

This submission is comprised of one clinical trial and therefore, integrated summaries of efficacy and safety were not warranted nor submitted.

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

The following sections were assigned to and reviewed in detail by the clinical reviewer.

Table 2: BLA Components Reviewed by the Clinical Reviewer

Module	Section/Study
5.3.5.1	Clinical study report and supportive documents for V920-016
5.3.5.1	Protocol for proposed Study V920-016
5.3.5.1	V920-016: CSR and supporting materials pertinent to safety data and analyses (Case Report Forms and Data Analysis)

Source: FDA-generated table
Abbreviations: BLA=Biologics License Application; CSR=clinical study report

Presented below are the amendment, modules and contents that were assigned to and reviewed by the clinical reviewer. The cover letters for each amendment were also reviewed.

- 125690/55.0 (received June 27, 2022):

  - Section 1 (Cover, Letter, Labeling, RMP, General Investigational Plan), Section 2 (Clinical Overview, Clinical Summary), Section 5 (Tabular Listing of all Clinical Studies, Clinical Study Reports, Literature References).
- 125690/55.3: September 29, 2022:
  - Section 1.14 (Labeling): Revised labeling that incorporates CBER's approved text per approval of STN 125690.51.
- 125690/55.4: October 14, 2022:
  - Section 1.11.3: (Clinical Information Amendment): Response IR dated September 16, 2022.
- 125690/55.6: November 30, 2022:
  - Section 1.11.3: (Clinical Information Amendment): Response to IR dated September 16. 2022, Updated Datasets.
- 125690/55.7: December 01, 2022
  - Section 1.11.3: (Clinical Information Amendment): Response to IR dated November 14, 2022, Updated Datasets.
- 125690/55.8: December 12, 2022
  - Section 5.3.5 (Reports of Efficacy and Safety Studies): Updated clinical datasets and reviewer's guide.
- 125690/55.9: February 14, 2023
  - Section 1.11.3 (Clinical Information Amendment): Correction of an error found in the review of the percentage of pediatric participants in the Ervebo group who shed vaccine virus post first vaccination.
- 125690/55.10: February 22, 2023
  - Section 1.14.1 (Draft Labeling): Updated PI that includes exact numbering (instead of rounded numbers) and correction to the value of shedding in children as described in the submission dated February 14, 2023.
- 125690/55.11: March 20, 2023
  - Section 1.11.3 (Clinical Information Amendment): Updated datasets to support correction of the percentage of pediatric participants who shed vaccine virus, based on the February 14, 2023 submission.
- 125690/55.12: April 04, 2023
  - Section 1.14.1 (Draft Labeling): Updated PI that includes changes in Sections 1 through 8.4.
- 125690/55.13: April 19, 2023
  - Section 1.14.1 (Draft Labeling): Updated PI based on revisions and comments, including deletions in clinical studies Sections 14 and deletion of the second dose information.
- 125690/55.14: April 24, 2023
  - Section 1.14.1 (Draft Labeling): Updated PI with results from PREA PMR study A-016 in Section 14.

5.3 Table of Studies/Clinical Trials

Table 3. Clinical Trial Included in the sBLA Submission

Study Number Number of Study Sites (Countries)	**Study Sponsors**	**Design**	**Number of Randomized Participants by Intervention Group (Ervebo and Placebo)**	**Study Population**	**Key Endpoints**
V920-016 6 sites (4 countries: Guinea, Liberia, Mali, and Sierra Leone)	National Institute of Allergy and Infectious Diseases, National Institutes of Health Institut National de la Santé et de la Recherche Médicale London School of Hygiene & Tropical Medicine	Phase 2, randomized, double-blind, placebo-controlled study of 3 vaccine strategies: 1-dose Ervebo 2-dose Ervebo Ad26.ZEBOV/ MVABN-Filo	Total participants: 2002 998 pediatric 1004 adults Overall Population (all ages): Pooled Ervebo [a]: n=1201 Ervebo 1 dose: n=802 Ervebo 2 dose: n=399 Pooled Placebo[b]: n=801 Participants 12 months through 17 years of age: Pooled Ervebo [a]: n=609 Ervebo 1 dose: n=407 Ervebo 2 dose: n=202 Pooled Placebo[b]: n=389 Participants ≥18 years of age: Pooled Ervebo[a]: n=592 Ervebo 1 dose: n=395 Ervebo 2 dose: n=197 Pooled Placebo[b]: n=412	Overall Population (all ages): Male: n=1094 Female: n=908 Median age: 18.0 Participants 12 months through 17 years of age: Male: n=546 Female: n=452 Median age: 8.0 Participants ≥18 years of age: Male: n=548 Female: n=456 Median age: 27.0	Immunogenicity: GP-ELISA (primary) and PRNT at baseline and Day 28, Month 3, and Month 12 Safety: Through 7-, 14- and 28-days post first vaccination: Solicited injection-site AEs[c], solicited systemic AEs[c] of any grade severity, unsolicited Grade 3 or 4 AEs

Source: FDA-generated table
Abbreviations: sBLA=supplemental Biologics License Application; AE=adverse event; GP-ELISA=glycoprotein enzyme-linked immunosorbent assay; PRNT=plaque reduction neutralization test
[a] Pooled Ervebo = Ervebo 1 dose or 2 dose.
[b] Pooled Placebo=0.5- and 1.0-mL placebo groups.
[c] Solicited injection-site AEs are referred to as injection-site reactions and solicited systemic AEs are referred to as targeted symptoms in the tables in this clinical overview.

5.4 Consultations

No outside consultations were obtained.

5.5 Literature Reviewed

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6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1

V920-016 (NCT02876328)
Partnership for Research on Ebola VACcinations (PREVAC):

A Phase 2, multi-center, randomized, double-blind, placebo-controlled trial to evaluate the safety and immunogenicity of Ervebo in pediatric participants 12 months through 17 years, and adult participants 18 years and older.
First participant, first visit: July 24, 2017
Last participant, data cut-off: December 24, 2019
Merck Sharp & Dohme (MSD) Database Lock Date: November 01, 2021.

Reviewer Comment: *As per Section 5.1 Review Strategy the original study protocol was amended four times, with 2002 Ervebo recipients enrolled in version 4.0.*

6.1.1 Objectives

Primary Objectives (relevant to the Ervebo one-dose regimen)

In Pediatric Participants 12 Months Through 17 Years of Age:

- To demonstrate that Ervebo (pooled Ervebo group) is superior to placebo (1-mL group) for the antibody response (glycoprotein enzyme-linked immunosorbent assay geometric mean titer (GP-ELISA GMT) on Day 28 after randomization (first vaccination).
- To demonstrate that Ervebo (1-dose group) is superior to placebo (1-mL group) for the antibody response (GP-ELISA) at Month 12 after randomization (first vaccination).

In Pediatric Participants 12 Months Through 17 Years of Age Versus Adult Participants 18 Years and Older:

- To demonstrate that Ervebo (pooled Ervebo group) is noninferior in pediatric participants 12 months through 17 years of age compared with adults 18 years and above for antibody response (GP-ELISA GMT) on Day 28 after randomization (first vaccination).

Reviewer Comment: *If met, the primary immunogenicity objective that compared the antibody response (GP-ELISA GMT) in pediatric participants to adult participants at Day 28 postvaccination would allow the Applicant to bridge the pediatric immunogenicity data to the adult efficacy data that served as the basis for the original licensure of Ervebo and support expansion of the use of Ervebo to pediatric subjects 12 months of age and older.*

Secondary Objectives
In pediatric versus adult participants:

- To demonstrate that pooled Ervebo is noninferior in pediatric participants 3 to 17 years of age compared with adults for antibody response (GP-ELISA GMT) on Day 28 after randomization (first vaccination)
- To demonstrate that pooled Ervebo is noninferior in pediatric participants 1 to 17 years of age compared with adults for antibody response (GP-ELISA GMT) on Day 28 after randomization (first vaccination)
- To summarize the percent difference for ELISA seroresponse (≥2-fold increase from baseline and ≥200 EU/mL, and ≥4-fold increase from baseline) between adults and children at Day 28 with the associated 95% CI

Select Secondary Objectives
In pediatric and adult participants:

- To summarize pooled Ervebo groups and placebo (1 mL) group antibody response profiles (GP-ELISA and plaque reduction neutralization test [PRNT] at baseline, Day 28, Month 3 and Month 12 after randomization (first vaccination).

- To determine the safety and tolerability of Ervebo through one-year postvaccination
- To summarize pooled Ervebo groups and pooled (0.5 and 1 mL) placebo groups, serious adverse events (SAEs) including death before Day 56, from Day 56 to Month 12 and Day 1 to Month 12.
- To summarize pooled Ervebo groups and pooled (0.5 and 1 mL) groups injection-site reactions and targeted symptoms, solicited AEs (including joint events), at the vaccination visit, and on Days 7, 14, and 28 after randomization (first vaccination), including daily contacts for children only.
- To summarize pooled Ervebo groups and pooled placebo (0.5 and 1 mL) groups unsolicited AEs.

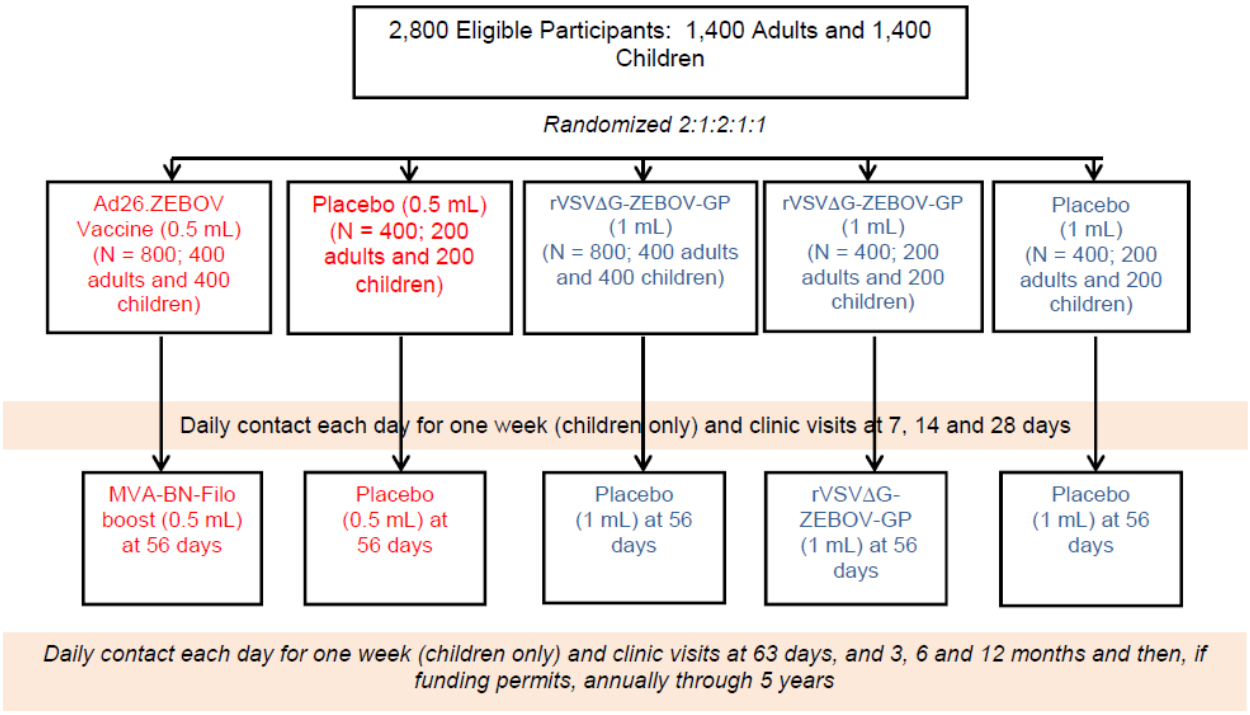
In pediatric participants only

- To summarize pooled Ervebo groups and pooled placebo groups (0.5 and 1 mL groups) changes from baseline in biochemical markers and complete blood count (CBC) measurements by clinical significance (if available) on Days 7, and 63 after randomization (first vaccination).
- In a subsample of children, to summarize separate and pooled Ervebo groups and 1 mL placebo groups for shedding saliva of VSV-ZEBOV at Days 7, 14, 28, 56, 63, and Month 3.

6.1.2 Design Overview

Study V920-016 is a phase 2, multicenter, randomized, double-blind, placebo-controlled safety and immunogenicity study of two Ebola vaccine candidates and three vaccine dosing regimens in pediatric (12 months and older) and adult participants. The vaccines were administered intramuscularly. The study was conducted in Guinea, Liberia, Mali and Sierra Leone.

Figure 1: PREVAC (V920-016) Study Design, Protocol Version 4



Source: STN 125690, Statistical Analysis Plan (SAP), page 7

Reviewer Comment: *As mentioned in Section 5.1 Review Strategy, the data from the Ad26.ZEBOV/MVA-BN-Filo treatment group were not included in this submission and will not be referred to further in this review.*

Randomization for Ervebo followed a 1:2:1:1 ratio (Ad26.ZEBOV/MVA-BN-Filo matching placebo: 1-dose V920: 2-dose V920: V920 matching placebo). Participants were stratified by age group (12 months to 17 years of age versus 18 years and older) and by the six study sites in four countries.

Study enrollment started with adults and pediatric participants ≥12 to ≤17 years of age. The next pediatric age subgroup of ≥5 to ≤11 years of age were enrolled after 70 participants aged ≥12 to ≤17 years were followed for 28 days, followed by the last age subgroup (12 months to 4 years of age) in a similar way. An independent data safety monitoring board (DSMB) reviewed the safety data for the initial pediatric age subgroups prior to allowing enrollment of the targeted 1,400 pediatric participants.

Reviewer Comment: *The sBLA contains safety and immunogenicity data for the 12 months following a single dose of Ervebo. A five-year extension study to evaluate the durability of the immune responses and SAEs through 60 months postvaccination is currently ongoing.*

Reviewer Comment: *Although pediatric subjects were enrolled per the age groups as described above, age sub-groups (i.e. <3 years, 3-11 years, 12-17 years) were used for the safety and immunogenicity analyses aligning with usual pediatric age strata employed in U.S. IND studies and per the sponsor "to provide greater specificity for understanding the immunogenicity and safety of V920 in children in regard to age".*

Blood samples for immunogenicity testing were obtained at baseline prior to vaccination, Day 28, Month 3, and Month 12 for all randomized participants. Safety was assessed from first vaccination through Month 12. A single-site sub-study was conducted in Guinea to quantify vaccine virus shedding and estimate the proportion of pediatric participants who shed vaccine virus in saliva.

6.1.3 Population

Inclusion Criteria:

- Planned residency in the area of the study site for the next 12 months and willingness to comply with the protocol requirements

Exclusion Criteria:

- Fever >38º Celsius
- History of EVD (self-report)
- Pregnancy (a negative urine pregnancy test is required for females of childbearing potential, i.e., females who have experienced menarche or who are aged 14 years and older)
- Positive human immunodeficiency virus (HIV) test for participants <18 years of age
- Reported current breast-feeding
- Prior vaccination against Ebola (self-report)
- Any vaccination in the past 28 days or planned within the 28 days after randomization (initial vaccination)
- In the judgement of the clinician, any clinically significant acute/chronic condition which would limit the ability of the participant to meet the requirements of the study protocol

6.1.4 Study Treatments or Agents Mandated by the Protocol

rVSVΔG-ZEBOV-GP (Ervebo)
The rVSVΔG-ZEBOV-GP vaccine (Ervebo, Ebola Zaire Vaccine Live), is a live-attenuated recombinant viral vaccine that is comprised of recombinant vesicular stomatitis virus (rVSV) in which the vesicular stomatitis virus (VSV) envelope glycoprotein G has been deleted and replaced with corresponding envelope glycoprotein of the *Zaire ebolavirus* (Kikwit strain). The vaccine is a sterile, aqueous, buffered solution supplied in a single-dose vial (1 mL/dose) configuration, and delivered by intramuscular (IM) injection.

Sterile Normal Saline
The placebo was a sterile normal saline (sodium chloride 0.9 percent for injection, (b) (4) , preservative free).

Reviewer Comment: *The approved vaccine formulation and dose was evaluated in both the pediatric and adult study populations.*

6.1.5 Directions for Use

A single 1-mL dose of the vaccine was administered intramuscularly in the arm or thigh for pediatric participants. The vaccine or placebo was administered in the upper arm for adults.

6.1.6 Sites and Centers

Study V920-016 was conducted by 5 investigators at 6 centers: 2 in Guinea, 1 in Liberia, 1 in Sierra Leone, and 2 in Mali.

Table 4. Number of Participants at the Clinical Sites, All Randomized, Study V920-016, Protocol Version 4

Site #	Country	Ervebo 1 Dose (N=802)	Ervebo 2 Dose (N=399)	Pooled Ervebo (N=1,201)[a]	Pooled Placebo (N=801)[b]	Total
-0001	Guinea	162	81	243	161	404
-0002	Guinea	124	62	186	124	310
-0003	Liberia	136	68	204	136	340
-0004	Sierra Leone	202	101	303	203	506
-0005	Mali	86	42	128	86	214
-0006	Mali	92	45	137	91	228

Source: Adapted from Applicant CSR, Table 14.1-4, page 226
Abbreviations: N=Number of participants randomized in the vaccination group.
[a] Pooled Ervebo = Ervebo 1 dose or 2 dose
[b] Pooled Placebo = 0.5 and 1.0 mL placebo groups

6.1.7 Surveillance/Monitoring

All subjects were followed for:

- solicited injection site reactions
  - pain/tenderness
  - redness
  - swelling/induration
  - itching
- solicited targeted systemic adverse reactions
  - reduced activity/somnolence
  - fatigue
  - vomiting
  - chills
  - abnormal sweating
  - skin lesions (macules, papules, purpura, petechia)
  - mouth ulcers
  - decreased appetite
  - feverishness
  - diarrhea
  - nausea headache
  - dizziness
  - abdominal pain
  - muscle pain
  - joint swelling
  - joint pain
  - in non-verbal children: irritability/fussiness, crying, and screaming

All solicited local and systemic adverse reactions were considered related to study intervention per the study protocol.

Grades 1 – 4 solicited adverse reactions, and Grades 3 – 4 unsolicited AEs were collected and recorded on the participant's case report forms (CRFs) on Days 7, 14, and 28 post first vaccination.

All subjects were followed for serious AEs (SAEs) including death and Ebola virus disease (EVD) through Month 12 post first vaccination. EVD and laboratory-confirmed malaria events that did not require hospitalization were not considered SAEs. Malaria events and body temperature measurements were obtained from all participants at Day 7, 14, Months 6 and 12 post first vaccination. Pediatric participants were assessed for injection site reactions, targeted systemic symptoms, SAEs, and body temperature at the following timepoints post first vaccination: daily contacts (Days 1 through 6) and study visits (Day 7, 14, Months 6 and 12) . Participants did not record daily temperatures outside of the scheduled visits but were queried regarding feverishness since their last visit. Elevated temperatures measured at study visits were reported as AEs of pyrexia, while feverishness was considered a solicited systemic adverse reaction.

Reviewer Comment: *All solicited adverse reactions and AEs were collected verbally at study visits using CRFs; diary cards were not provided. This may have affected recall and overall reporting of events. However, any recall bias would be expected to be distributed equally between the vaccine and placebo groups.*

Safety laboratory assessments consisting of complete blood count (CBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), bilirubin and creatinine were performed at baseline for all participants and at Day 7 and Day 63 for pediatric participants.

Reviewer Comment: *Safety laboratory assessments were performed as described above and clinically significant laboratory abnormalities were followed until they returned to normal, or a satisfactory clinical explanation had been provided.*

Concomitant medications/vaccinations were not collected or recorded, except for postvaccination antipyretic usage for fever and pain relief.

Pregnancy testing was required at the time of screening and participants who reported becoming pregnant post first vaccination visit through the Month 3 visit were followed for pregnancy outcomes.

Viral shedding was assessed at baseline, and Days 7, 14, 28, 56, 63 and Month 3 post first vaccination.

An independent DSMB monitored safety. The DSMB was to recommend a study pause in the event of a death or SAE that was considered vaccine-related and to either pause the study or request that participants be notified in the event of increased frequency of unanticipated AEs. The DSMB also reviewed completeness of follow-up and study conduct. The DSMB was to issue a recommendation to either continue the study as planned or continue with modifications after each meeting. Per the protocol's strategy for sequentially enrolling increasingly younger pediatric participants, the DSMB reviewed pediatric safety data at least monthly before moving to less frequent reviews when no safety concerns were identified.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoints:

- Ebola virus glycoprotein (GP-EBOV) antibody response at Day 28 after randomization (first vaccination), as measured by GP-ELISA
- GP-EBOV antibody response at Month 12 after randomization (first vaccination), as measured by GP-ELISA (primary immunogenicity endpoint)

The study success criterion based on immunogenicity in the pooled Ervebo group was the lower bound (LB) of the 2-sided 95% CI of the pooled Ervebo GP-ELISA GMT response ratio in pediatric/adult participants is >0.5 for the antibody response at Day 28 post first vaccination. The prespecified non-inferiority margin was 0.5.

The primary analysis for adults and pediatric participants was performed on those who did not have elevated antibody levels at baseline.

Reviewer Comment: *To ascertain the effectiveness of Ervebo in pediatric participants 12 months through 17 years of age, immunogenicity assessments that bridged the GP-ELISA GMT antibody response of pediatric participants to adult participants at Day 28 post first vaccination was conducted using non-inferiority analyses.*

Secondary Endpoints

Main Secondary Endpoints:

- GP-EBOV antibody response at Day 28, Month 3, and Month 12 after randomization (first vaccination) as measured by GP-ELISA (secondary immunogenicity endpoint)
- Neutralizing antibody response at Day 28, Month 3, and Month 12 after randomization (first vaccination), as measured by PRNT (secondary immunogenicity endpoint)
- SAEs, including death, occurring through Month 12
- Injection-site reactions and targeted symptoms of any grade severity and Grade 3 or 4 unsolicited AEs post first vaccination and through 7, 14, and 28 days post first vaccination

Other Secondary Safety Endpoints:

- Maximum intensity of injection-site reactions and targeted solicited systemic reactions
- Vaccine-related AE
- Changes in vital signs (e.g., temperature
- Changes in body measurement (children only)
- Clinically significant changes from baseline in biochemical markers and CBC measurements (children only)
- Shedding in saliva of rVSVΔG-ZEBOV-GP recombinant virus through Month 3 (subsample of children)

Reviewer Comment: *This clinical review focuses on the primary immunogenicity endpoint as well as all safety endpoints.*

6.1.9 Statistical Considerations & Statistical Analysis Plan

The study was powered (n=2800) to compare the safety and immunogenicity outcomes in adults (N=1400) and pediatric (N=1,400) participants separately. The saliva sub-study had a

target sample size of 140 pediatric participants, with approximate equal distribution of participants in each of the three pediatric age sub-groups.

All primary and secondary non-inferiority immunogenicity hypotheses had >99% power except the first secondary immunogenicity hypothesis (non-inferiority test using a margin of 0.67) which had a least 96% power for sample sizes down to 38 pediatric participants (3 to 17 years age group) vs. 885 adults (18 years and older) vaccinated with Ervebo. It was assumed that the sample size will allow at least 99% power to detect a 4% difference between Ervebo and placebo (5% vs 1%).

Of the approximately 2186 pediatric participants enrolled, approximately 1248 were expected to receive Ervebo (1 or 2 doses) or placebo (1 mL). The minimum number of pediatric participants for the study was targeted to be approximately 1000 with an expected 20% unevaluable data (e.g., dropout, missing samples, etc.) based on prior clinical trial experience.

Reviewer Comment: *The Applicant did not pre-specify an attrition rate that would prompt a more conservative population analysis. However, the Applicant did conduct a post-hoc sensitivity analysis of the full PP population including any vaccinated participant with baseline serostatus and no protocol violations.*

The immunogenicity assessments were conducted on the GP-ELISA per-protocol (PP) population. See Section 6.1.10.1 for definitions of study populations.

Analyses of antibody titers for the primary and secondary objectives were conducted by log-transforming the data from the Ervebo and 1-mL placebo groups and performing analysis of variance (ANOVA) on the log-transformed data. The ANOVA model included treatment groups as a covariate. A fixed sequence test was used to test five immunogenicity hypotheses to control the overall type 1 error at $\alpha = 0.025$ (1-sided). Summary statistics (counts and percentages) was used to evaluate safety.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The protocol pre-specified the populations for the immunogenicity and safety analyses.

Per Protocol (PP) Population

The per-protocol (PP) population is the primary population for the analysis of immunogenicity in the PREVAC study. The PP immunogenicity population consisted of all randomized and vaccinated participants who:

1. Met inclusion criteria
2. Did not meet exclusion criteria
3. Had baseline serology data, seronegative (enzyme-linked immunosorbent assay [ELISA] < 200 EU/mL) and seropositive (ELISA ≥ 200 EU/mL)
4. Received 1-dose Ervebo, 2-dose Ervebo, or 1 mL placebo (Ervebo matching placebo)
5. Did not have major protocol deviations

GP-ELISA PP Immunogenicity Population
A subset of the PP population that excluded participants with protocol violation (due to missing, unevaluable, or out of day range serology samples/results) was used for the primary immunogenicity analysis. Results that were identified as quantity not sufficient and/or indeterminant were not included in the analyses.

All Participants as Treated (APaT) Population
The APaT was the primary population for the safety analyses and consisted of all randomized participants who received at least 1 dose of Ervebo or placebo (0.5 mL or 1 mL) and had follow-up at at least one defined timepoint. The pooled Ervebo used for safety analyses in comparison to placebo included only subjects that received one dose of Ervebo at the Day 28 post first vaccination timepoint, when solicited events were assessed. The second dose group did not receive the second dose of Ervebo until Day 56 post first vaccination.

Reviewer Comment: *The 1-mL placebo was used as a matched control for the 1-mL Ervebo vaccine in the immunogenicity analyses. Whereas the Applicant pooled the placebo doses (0.5 mL and 1 mL) to increase the number of participants in the placebo group for comparison to the pooled Ervebo group used in the safety analyses.*

6.1.10.1.1 Demographics

The following table shows the demographic characteristics of participants who received Ervebo in Study V920-016 under protocol version 4.0.

Table 5: Demographics of Participants in Study V920-016, Protocol Version 4.0

Demographic	Ervebo 1 Dose N=802 n (%)	Ervebo 2 Dose N=399 n (%)	Pooled Ervebo[a] N=1201 n (%)	Pooled Placebo[b] N=801 n (%)	Total N=2002 n (%)
Sex, n (%)	--	--	--	--	--
Male	435 (54.2)	227 (56.9)	662 (55.1)	432 (53.9)	1094 (54.6)
Female	367 (45.8)	172 (43.1)	539 (44.9)	369 (46.1)	908 (45.4)
Age (years) All, n (%)	--	--	--	--	--
<18	407 (50.7)	202 (50.6)	609 (50.7)	389 (48.6)	998 (49.9)
≥18	395 (49.3)	197 (49.4)	592 (49.3)	412 (51.4)	1004 (50.1)
18–65	386 (48.1)	194 (48.7)	580 (48.3)	406 (50.7)	986 (49.3)
>65	9 (1.1)	3 (0.8)	12 (1.0)	6 (0.7)	18 (0.9)
Mean,	19.7	18.8	19.4	19.8	19.6
Median	17.0	17.0	17.0	18.0	18.0
Range	1 - 74	1 - 72	1 - 74	1 - 76	1 – 76
Age (years) Pediatric participants, n (%)	--	--	--	--	--
<3	56 (13.8)	39 (19.3)	95 (15.6)	60 (15.4)	155 (15.5)
3–11	213 (52.3)	97 (48.0)	310 (50.9)	205 (52.7)	515 (51.6)
12–17	138 (33.9)	66 (32.7)	204 (33.5)	124 (31.9)	328 (32.9)
Mean	8.6	8.2	8.4	8.3	8.4
Median	9.0	8.0	9.0	8.0	8.0
Range	1 -17	1 - 17	1 - 17	1 - 17	1 - 17

Demographic	Ervebo 1 Dose N=802 n (%)	Ervebo 2 Dose N=399 n (%)	Pooled Ervebo[a] N=1201 n (%)	Pooled Placebo[b] N=801 n (%)	Total N=2002 n (%)
HIV status, n (%)	--	--	--	--	--
Negative	789 (98.4)	397 (99.5)	1186 (98.8)	797 (99.5)	1983 (99.1)
Positive	13 (1.6)	2 (0.5)	15 (1.2)	4 (0.5)	19 (0.9)
BMI (Mean)	--	--	--	--	--
All	20.1	19.9	20.0	20.1	20.0
Adults	23.7	23.5	23.6	23.5	23.6
Pediatric participants	16.6	16.4	16.5	16.4	16.5

Source: Adapted from sBLA 125690/55; Clinical Study Report Table 10-5 and 10-6, page 117 - 120.
Abbreviations: BMI=body mass index; sBLA=supplemental Biologics License Application
[a] Pooled Ervebo = Ervebo 1 dose or 2 dose
[b] Pooled Placebo = 0.5 and 1.0 mL placebo groups

Race and concomitant medications/vaccinations were not collected.

Reviewer Comment: *Approximately half of the randomized participants in the overall population were male (54.6%) and younger than 18 years (54.7%). The one percent of participants who were HIV-positive were all adults. Among pediatric participants, the mean age was 8 years and about half (51.6%) were in 3 -11 years of age. Among adult participants, the mean age was 20 years and 98% were between the ages of 18 and 65 years.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Baseline Serostatus

Table 6 below shows the GP-ELISA baseline serostatus of the pediatric participants by vaccine dose.

Table 6. Baseline GP-ELISA Serostatus in the Pediatric Participants

Serostatus	Ervebo 1 Dose	Pooled Ervebo[a]	Placebo[b]
Pediatrics	**N=386 n (%)**	**N=581 n (%)**	**N=203 n (%)**
<200 EU/mL (seronegative)	263 (68.1)	392 (67.5)	130 (64.0)
≥200 EU/mL (seropositive)	66 (17.1)	99 (17.0)	40 (19.7)
Missing	57 (14.8)	90 (15.5)	33 (16.3)
Adults	**N=386 n (%)**	**N=580 n (%)**	**N=187 n (%)**
<200 EU/mL (seronegative)	282 (73.1)	418 (72.1)	147 (78.6)
≥200 EU/mL (seropositive)	95 (24.6)	146 (25.2)	36 (19.3)
Missing	9 (2.3)	16 (2.8)	4 (2.1)

Source: Adapted from sBLA 125690/55; Clinical Study Report Table 14.1-11, pages 241 & 243.
Abbreviations: GP-ELISA=glycoprotein enzyme-linked immunosorbent assay; PP=per-protocol; PRNT=plaque reduction neutralization test
[a] Pooled Ervebo = Ervebo 1 dose or 2 dose
[b] Placebo = 1 mL placebo groups

Reviewer Comment: *The baseline GP-ELISA serostatus in the pediatric and adult population was similar between treatment groups. Approximately 15% of pediatric participants had missing GP-ELISA serostatus compared to 2% of adults. The missing values in the pediatric population was mostly due to inability to draw blood by phlebotomy or clotted blood that did not allow for hematology analyses.*

The Applicant did not collect other baseline medical history. The protocol specified that enrolled participants were to be free of any significant acute or chronic conditions which would limit the ability to participate in study requirements.

Reviewer Comment: *The PREVAC study did not collect baseline medical history, similar to the study that evaluated Ervebo vaccine efficacy in adults.*

6.1.10.1.3 Participant Disposition

PREVAC, protocol version 4.0, enrolled a total of 2802 participants, 2002 participant were randomized to receive either Ervebo (n = 1201) or placebo (n = 801). The remaining 800 were randomized to the Ad26.ZEBOV/MVA-BN-Filo arm. Of the 1201 participants randomized to Ervebo, 609 were pediatric and 592 were adult participants. Of the 801 participants randomized to placebo 389 were pediatric and 412 were adult participants.

Table 7 below summarizes the disposition of all randomized participants under protocol version 4.0.

Table 7: Disposition of All Randomized Participants, Protocol Version 4.0

Disposition	Ervebo 1 Dose N=802 n (%)	Pooled Ervebo[a] N=1201 n (%)	Pooled Placebo[b] N=801 n (%)
Vaccination 1	802 (100)	1201 (100)	800 (100)
Vaccination 2	761 (94.9)	1146 (95.4)	773 (96.5)
Completed	773 (96.4)	1153 (96.0)	766 (95.6)
Discontinued	29 (3.6)	48 (4.0)	35 (4.4)
Death	6 (0.7)	6 (0.5)	3 (0.4)
Lost to follow-up	2 (0.2)	5 (0.4)	4 (0.5)
Withdrawal by subject	4 (0.5)	8 (0.7)	4 (0.5)
Other	17 (2.1)	29 (2.4)	24 (3.0)

Source: Adapted from sBLA 125690/55; Clinical Study Report Table 10-1, page 109.
Abbreviations: sBLA=supplemental Biologics License Application
[a] Pooled Ervebo = Ervebo 1 dose or 2 dose
[b] Pooled placebo = 0.5 and 1.0 mL placebo groups

Table 8 below shows the disposition of all randomized pediatric participants 12 months through 17 years under protocol version 4.0

Table 8. Disposition of All Randomized Pediatric Participants, Protocol Version 4.0

Disposition	Ervebo 1 Dose N=407 n (%)	Pooled Ervebo[a] N=609 n (%)	Pooled Placebo[b] N=389 n (%)
Vaccination 1	407 (100)	609 (100)	389 (100)
Vaccination 2	396 (97.3)	594 (97.5)	381 (97.9)
Completed	395 (97.1)	587 (96.4)	377 (96.9)
Discontinued	12 (2.9)	22 (3.6)	12 (3.1)
Death	3 (0.7)	3 (0.5)	2 (0.5)
Lost to follow-up	0 (0.0)	1 (0.2)	1 (0.3)
Withdrawal by subject	1 (0.2)	2 (0.3)	2 (0.5)
Other	8 (2.0)	16 (2.6)	7 (1.8)

Source: Adapted from sBLA 125690/55; Clinical Study Report Table 14.1-2, page 223.
Abbreviations: sBLA=supplemental Biologics License Application
[a] Pooled Ervebo = Ervebo 1 dose or 2 dose
[b] Pooled placebo = 0.5 and 1.0 mL placebo groups;

A majority (95.9%) of the randomized participants received both vaccinations to which they were randomized and completed the study. Two participants received the incorrect study intervention and were excluded from the immunogenicity and safety analyses population that evaluated Ervebo . The first participant received 1 dose of AD26ZEBOV + placebo instead of Ervebo + placebo and the second participant received placebo + MVA instead of placebo + placebo.

Reviewer Comment: *The rate of study completion (≥95%) was similar across the vaccination groups and between the pediatric and adult participants. The percentage of participants who discontinued from the study and the reason for discontinuation were similar between vaccination groups overall (Ervebo 1-dose – 29/802 (3.6%), pooled Ervebo -48/1201(4.0) and pooled placebo - 35/801 (4.4%) and between pediatric (34/998 – 3.4%) and adult (49/100 – 4.9%) participants. Overall, the number of participant discontinuations was generally low (3-5%) in adults and pediatric participants and in Ervebo and placebo groups. No participant discontinued the study due to an AE or SAE.*

GP-ELISA Immunogenicity Analyses Population

GP-ELISA immunogenicity analyses were conducted on 96.8% (1551/1602) of the PP population. Participants with missing, unevaluable or lack of day range serology samples were excluded from analysis.

Table 9 below shows the overall disposition of participants in the GP-ELISA immunogenicity PP population.

Table 9. Disposition of Participants Accounting for the GP-ELISA in the PP Immunogenicity Population by Vaccination Group (All Randomized or Enrolled Participants, Protocol Version 4.0)

Disposition	Ervebo 1 Dose N=802 n (%)	Pooled Ervebo N=1201[a] n (%)	Placebo N=401[b] n (%)
Number of vaccinated participants	802 (100.0)	1201 (100.0)	401 (100.0)
Number of vaccinated participants with no serology data	0 (0.0)	1 (0.1)	0 (0.0)
Number of participants excluded from GP-ELISA PP population	30 (3.7)	39 (3.2)	11 (2.7)
Total # of participants included in GP-ELISA PP population	772 (96.3)	1161 (96.7)	390 (97.3)
Reasons for exclusion from GP-ELISA PP population	--	--	--
Protocol violation	29 (3.6)	38 (3.2)	11 (2.7)
Cross treatment	1 (0.1)	1 (0.1)	0 (0.0)

Source: Adapted from sBLA 125690/55; Clinical Study Report Table 10-3, page 114.
Abbreviations: sBLA=supplemental Biologics License Application; GP-ELISA=glycoprotein enzyme-linked immunosorbent assay; PP=per-protocol; N=number of participants randomized to the respective intervention group
[a] Pooled Ervebo = Ervebo 1 dose or 2 dose;
[b] Placebo = 1-mL placebo group

Protocol Deviations

The Applicant defined a protocol deviation as the failure to comply with applicable protocol, standard operating procedures, regulatory requirements, or institutional review board requirements for the protection of human participants or the integrity of study data. Deviations were characterized as serious (i.e., increases risk, cause harm or decreases potential for participants, or invalidates study data), or nonserious. The Applicant further defined important protocol deviations as deviations that may significantly impact the quality or integrity of key study data or significantly affect a subject's rights, safety, or well-being.

Major protocol deviations reported in the study are summarized in Table 10 below.

Table 10: Major Protocol Deviations, Protocol Version 4.0

Participant Group	Ervebo 1 Dose N=802 n (%)	Ervebo 2 Dose N=399 n (%)	Pooled Ervebo[a] N=1201 n (%)	Pooled Placebo[b] N=801 n (%)
Participants with deviation	29 (3.6)	9 (2.3)	39 (3.2)	11 (1.4)
Other deviation	21 (2.6)	7 (1.8)	28 (2.3)	20 (2.5)
ICF/ICF process	4 (0.5)	1 (0.3)	5 (0.4)	4 (0.5)
Involves a minor child	19 (2.4)	5 (1.3)	24 (2.0)	13 (1.6)
Meets the definition of an UP	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Missing initial ICF	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Participants randomized did not meet all eligibility criteria	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Pregnancy test result not obtained prior to vaccine	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Required labs not obtained	6 (0.7)	1 (0.3)	7 (0.6)	4 (0.5)
Serious NC	4 (0.5)	1 (0.3)	5 (0.4)	2 (0.3)

Source: Adapted from STN 125690.55 Clinical Study Report, Table 14.1-19, page 257 and ADPDEV dataset
Abbreviations: ICF=informed consent form; NC=nonconformity; UP=unanticipated problem
[a] Pooled Ervebo = Ervebo 1 dose or 2 doses
[b] Pooled placebo = 0.5 and 1.0 mL placebo groups

Less than 4% of participants in each study vaccine group experienced one or more protocol deviations, with 2.1% of the reported protocol deviations in children. The most frequently reported type of protocol deviation was “other deviation.” The category of “other deviation” included the following:

- A postvaccination observation that lasted <30 minutes
- A missing or an abnormal test result not transmitted by the laboratory to the investigator, a failure to retest a Grade 3 laboratory test result, or use of the wrong normal range
- An out of window visit and the reporting of a Grade 3 laboratory test result, pregnancy or pregnancy outcome outside the required timeframe
- The entering of an SAE in the electronic case report form (eCRF) >24 hours after it was reported, the failure of a site to notify the sponsor of a SAE or death within 24 hours of learning of the event, the failure of an investigator to sign off on a SAE or pregnancy entered in the eCRF.
- Administration of the wrong second vaccination.
- A violation of the eligibility criteria
- A kit identification discrepancy, or use of the wrong sampling kit (i.e., mixing a child sampling kit for an adult kit)
- The collection of an additional blood sample, failure to collect a sample (e.g., saliva) or insufficient blood volume collection
- The on-site loss of an informed consent form (ICF).
- An inconsistency between the ICF checkbox and day 0 notes on a subject’s childbearing potential

Eight serious protocol deviations were reported in the study as follows:

- 3 participants received an incorrect study vaccination regimen
- 2 participants with SAEs declared on the eCRF >24 hours after site awareness
- 1 participant was randomized despite not meeting eligibility criteria
- 1 participant’s childbearing potential was inconsistently recorded in their eCRF (participant subsequently confirmed to be postmenopausal per Applicant).
- 1 death was not reported within 24 hours

All but one of the serious protocol deviations identified were classified as important by the Applicant: the participant randomized despite not meeting the eligibility criteria. The participant was found not to have an ICF during an on-site monitoring visit. The subject’s data was excluded from all of the analyses in the study. The inconsistency in the reporting of childbearing potential was not considered to be important because the participant was subsequently confirmed to be postmenopausal.

Reviewer Comment: *The rates of protocol deviations across vaccine groups were similar and generally low. The sponsor appears to have adequately addressed issues with good clinical practice compliance, ICF completion (where possible) and safety assessments.*

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Immunogenicity Endpoint(s)

The primary immunogenicity analysis that compared the noninferiority of pediatric vs adult GP-ELISA GMT antibody responses at 28 days after randomization was performed on a subset of the PP population that included all vaccinated participants with serology data who were

compliant with the protocol and had a serum sample collected within an acceptable day range. Results that were identified as quantity not sufficient and/or indeterminant were not included in the analysis.

To complete the primary immunogenicity analysis, 51/1602 (3.2%) participants were excluded from the PP population for missing, unevaluable, and out of day range sample/results. A sensitivity analysis of all participants in the PP population was also performed. See Section 6.1.11.5 for more details.

Table 11 below shows the summary of the primary endpoint analysis GMT for the GP-ELISA PP by dose and age.

Table 11**. Non-inferiority[a] Analysis of Pooled Geometric Mean Titers at Day 28 for the GP-ELISA PP Population**

Assay	Time Point	12 Months Through 17 Years of Age GMT n = 499 (95% CI)	18 Years of Age and Older GMT n = 519 (95% CI)	12 Months Through 17 Years / 18 Years and Older GMT[b] Ratio (95% CI)	12 Months Through 17 Years / 18 Years and Older Met Noninferiority Objective (Y/N)
GP-EBOV as measured by GP-ELISA	28 days post first vaccination	1,748.8 (1585.6, 1928.7)	1,234.4 (519) (1132.5, 1345.4)	1.42* (1.24, 1.62)	Y

Abbreviations: n=Number of participants contributing to the analysis; CI=Confidence interval; GMT=geometric mean titer; GP-ELISA=glycoprotein enzyme-linked immunosorbent assay.
[a] Non-inferiority is declared if the lower bound of the 2-sided 95% CI for the GMT ratio is greater than 0.5.
[b] GMT (individuals 12 months through 17 years of age) / GMT (individuals 18 years of age and older)

The primary immunogenicity outcome was met with the pooled pediatric population having a non-inferior immune response as compared to the pooled adult population with a LB of the GMT ratio 95% CI >0.5.

Reviewer Comment: *Analysis of the secondary immunogenicity endpoint using a less conservative noninferiority margin of 0.67 was also met. The results of the post hoc analysis conducted on the PP population, which consisted of all vaccinated participants with serology data and no protocol violation, were consistent with the results of the primary and secondary immunogenicity analyses.*

6.1.11.2 Analyses of Secondary Endpoints

PRNT analyses were conducted on 51.2% (821/1602) of the PP population, comprising samples from 100% (n=631) of the pediatric participants and a random sampling (n=190) of adult participants.

Reviewer Comment: *Emphasis was placed on analyzing more pediatric samples via PRNT assay than adult samples given that PRNT immune responses were secondary endpoints and the immunogenicity profile of Ervebo in adults had been characterized in previous clinical trials.*

Table 12 summarizes the GP-ELISA and PRNT GMT and GMFI results post 1 dose of Ervebo vaccination by study time point in pediatric participants.

Table 12. GP-ELISA and PRNT Geometric Mean Titer and Geometric Mean Fold-Rise Post First Vaccination (Pediatric Participants – GP-ELISA PP population)

Time Point	GP-ELISA GMT (n) [95% CI]	GP-ELISA GMFI (n) [95% CI]	PRNT GMT (n) [95% CI]	PRNT GMFI (n) [95% CI]
Baseline	100.3 (351) [90.6, 111.1]	--	17.7 (284) [17.2, 18.1]	--
Day 28	1,823.6 (336) [1,618.5, 2,054.7]	18.9 (313) [16.6, 21.5]	281.9 (266) [255.5, 311.0]	16.1 (245) [14.5, 17.8]
Month 3	1,282.1 (370) [1,168.6, 1,406.6]	12.8 (338) [11.4, 14.4]	161.1 (293) [149.4, 173.8]	9.4 (268) [8.6, 10.1]
Month 12	1,444.4 (284) [1,295.1, 1,610.9]	17.4 (250) [15.1, 20.1]	307.0 (205) [278.0, 339.1]	17.5 (191) [15.8, 19.5]

Source: Adapted from sBLA 125690/55; CSR Table 11-8, 11-11, 14.2-57, 2-88, 2-98, 2-108, page 138, 143, 341, 380, 391, 402
Abbreviations: sBLA=supplemental Biologics License Application; CI=confidence interval; GMFI=geometric mean fold increase; GMT=geometric mean titer; GP-ELISA=glycoprotein enzyme-linked immunosorbent assay; n=number of participants contributing to the analysis. Participant must have serology data at baseline and timepoint.

Table 13 is a summary of the GP-ELISA GMT and GMFI post 1 dose of Ervebo vaccination by study time point in adult participants.

Table 13. GP-ELISA and PRNT Geometric Mean Titer and Geometric Mean Fold-Rise Post First Vaccination (Adult Participants – GP- ELISA PP population)

Time Point	GP-ELISA GMT (n) [95% CI]	GP-ELISA GMFI (n) [95% CI]	PRNT GMT (n) [95% CI]	PRNT GMFI (n) [95% CI]
Baseline	140.2 (379) [129.0, 152.4]	--	17.5 (92) [16.7, 18.4]	--
Day 28	1,241.2 (343) [1,116.4, 1,380.0]	9.3 (338) [8.3, 10.4]	170.1 (98) [144.1, 200.7]	10.2 (89) [8.6, 12.1]
Month 3	1,068.5 (363) [971.7, 1,175.1]	7.8 (357) [7.0, 8.7]	111.3 (98) [96.3, 128.6]	6.7 (90) [5.7, 7.8]
Month 12	1,088.4 (292) [983.5, 1,204.6]	8.7 (289) [7.8, 9.8]	144.3 (84) [122.2, 170.4]	8.7 (78) [7.4, 10.2]

Source: Adapted from sBLA 125690/55; CSR Table 11-9, 11-12, 14.2-89, 2-99, pages 139, 144, 342, 381, 392.
Abbreviations: sBLA=supplemental Biologics License Application; CI=confidence interval; GMFI=geometric mean fold increase; GMT=geometric mean titer; GP-ELISA=glycoprotein enzyme-linked immunosorbent assay; n=number of participants contributing to the analysis.

Reviewer Comment: *Antibody responses in pediatric and adult participants following a single dose of Ervebo were similarly robust across all time points as measured by GP-ELISA and PRNT with pediatric participants having higher immune responses and fold increases as compared to adults at all time points. Not unexpectedly, GP-ELISA GMTs were 5- to 8-fold higher than PRNT GMTs at all time points in both pediatric and adult participants; however, it is reassuring that GP-ELISA and PRNT GMFIs were robust and similar at each measured time point.*

The Applicant also evaluated seroresponse rates by GP-ELISA (defined as ≥2-fold increase from baseline and ≥200 EU/mL postvaccination) and by PRNT (defined as a ≥4-fold increase in PRNT titer from baseline) in the study. The Applicant calculated that 92.2%/91.9% of vaccinated participants and 93.5% /94.4% of pediatric participants in the pooled Ervebo group met the GP-ELISA seroresponse definition at Day 28 and Month 12 postvaccination, respectively. The Applicant calculated that 91.0%/91.8% of vaccinated participants and 92.4%/95.8% of pediatric participants met the PRNT seroresponse definition at Day 28 and Month 12 postvaccination,

respectively. However, the clinical relevance of the values chosen to define the seroresponse is unclear, given no correlate of protection has been identified for Ervebo.

6.1.11.3 Subpopulation Analyses

Immunogenicity summaries by subgroups were provided for the GP-ELISA and PRNT to explore the impact of age, sex, and baseline serostatus for the Ebola antibody (based on the serostatus cutoff of 200 EU/mL for the GP-ELISA). The age subgroups included pediatric participants 12 months to <3, 3 to <12, and 12 to 17 years of age, pediatric participants 12 months through 17 years of age, and adults ≥18 years of age.

Table 14 describes the 1-dose Ervebo GP-ELISA GMT and GMFI for the overall PP study population, adults, pediatric, and by pediatric subgroups of age, sex and baseline serostatus at various study time points. in the GP-ELISA PP immunogenicity population.

Table 14. GP-ELISA Geometric Mean Titer and Geometric Mean Fold-Increase Post First Vaccination by Subgroup, PP

Subgroup	Baseline GMT (n) [95% CI]	Day 28 GMT (n) [95% CI]	Day 28 GMFI (n) [95% CI]	Month 3 GMT (n) [95% CI]	Month 3 GMFI (n) [95% CI]	Month 12 GMT (n) [95% CI]	Month 12 GMFI (n) [95% CI]
<3 years of age	50.2 (43) [40.2, 62.7]	1,192.1 (45) [827.6, 1,717.1]	23.8 (39) [15.5, 36.3]	1,092.3 (48) [847.9, 1,407.2]	22.7 (41) [16.4, 31.3]	1,719.3 (45) [1,245.7, 2,373.1]	38.9 (36) [26.5, 56.9]
3-11 years of age	93.3 (180) [80.6, 108.1]	1,845.1 (171) [1,552.1, 2,193.4]	21.0 (156) [17.4, 25.2]	1,286.5 (197) [1,127.6, 1,467.9]	13.3 (175) [11.4, 15.6]	1,368.4 (153) [1,189.3, 1,574.5]	16.9 (130) [13.9, 20.7]
12-17 years of age	140.0 (128) [120.9, 162.2]	2,103.3 (120) [1,772.2, 2,496.4]	15.3 (118) [12.7, 18.5]	1,356.1 (125) [1,177.5, 1,561.7]	10.0 (122) [8.3, 12.0]	1,451.6 (86) [1,188.6, 1,772.8]	12.9 (84) [10.3, 16.2]
Male	123.7 (404) [113.4, 135.0]	1,456.1 (365) [1,303.1, 1,627.2]	12.1 (353) [10.8, 13.6]	1,021.3 (392) [935.9, 1,114.4]	8.4 (376) [7.5, 9.3]	1,019.0 (293) [920.0, 1,128.7]	9.8 (275) [8.6, 11.1]
Female	114.2 (326) [103.1, 126.4]	1,556.0 (314) [1,383.7, 1,749.8]	14.3 (298) [12.5, 16.4]	1,371.7 (341) [1,237.0, 1,521.0]	12.1 (319) [10.7, 13.7]	1,547.9 (283) [1,387.1, 1,727.5]	14.9 (264) [13.0, 17.2]
Baseline GP-ELISA <200 EU/mL	89.8 (545) [86.6, 93.2]	1,423.4 (494) [1,304.3, 1,553.4]	16.2 (494) [14.8, 17.8]	1,092.5 (523) [1,014.0, 1,177.1]	12.3 (523) [11.3, 13.3]	1,175.5 (424) [1,081.8, 1,277.4]	14.0 (424) [12.8, 15.3]
Baseline GP-ELISA ≥200 EU/mL	414.4 (161) [363.1, 472.9]	1,931.4 (133) [1,614.5, 2,310.4]	4.5 (133) [3.8, 5.4]	1,382.3 (148) [1,195.6, 1,598.0]	3.4 (148) [2.9, 3.9]	1,498.2 (91) [1,212.9, 1,850.6]	3.5 (91) [2.9, 4.4]

Source: Adapted from sBLA 125690/55; Clinical Study Report. Tables 14.2-38, 2-39, 2-40, 2-41, 2-42, 2-43, 2-44, 2-45 2-46, 2-47, 2-48, 2-49, 2-50, 2-51, 2-52, 2-53, 2-54 and 2-55; Pages 320, 321, 322, 323, 324, 325, 326, 327, 329, 330, 331, 332, 333, 334, 335, 336, 337 and 338.
Abbreviations: CI=confidence interval; GMT=geometric mean titer; GMFI=geometric mean fold increase; GP-ELISA=glycoprotein enzyme-linked immunosorbent assay; N=number of participants with serology data at one or more timepoints according to the intervention randomized; n=number of participants contributing to the analysis. Participants must have serology data at baseline and timepoint.

Reviewer Comment: *The Day 28 GP-ELISA GMT was higher for pediatric participants than adults across all time points and highest in the 12 to 17 years of age subgroup for pediatric participants. The Day 28 GMFI was higher in pediatric participants than adults across all time points. The GMFI was generally higher for pediatric participants <3 years of age, compared with 3 to 11 and 12 to 17 years of age, suggesting that even the youngest pediatric participants are capable of mounting a robust humoral response to the 1-dose Ervebo vaccination. Females had consistently higher GMTs and GMFI rates than males*

It is unclear whether the high rate of baseline seropositivity (20.7% of participants) reflects assay variability or previous exposure to wild type Ebola or a related virus. While the GMTs were higher at every time point for baseline seropositive participants, the GMFI rates were, not unexpectedly, lower compared to baseline seronegatives.

The results of the subgroup analyses based on age, sex and baseline serostatus were consistent with the result of the non-inferiority analyses conducted on the primary immunogenicity endpoint.

Of note, the pattern of PRNT responses in each subgroup were generally similar to those seen for the GP-ELISA responses, with a higher magnitude of PRNT GMFI observed in pediatric participants younger than 3 years of age compared with pediatric participants 3 to 11 and 12 to 17 years of age.

6.1.11.4 Dropouts and/or Discontinuations

Most (95.9%) of participants that received both vaccinations to which they were randomized and completed the study. The percentage of participants who discontinued from the study and reasons for discontinuation were similar across the intervention groups. No participant discontinued from study intervention or the study due to an adverse event.

See Section 6.1.10.1.3 (Participant Disposition) for more information on dropouts and discontinuations.

6.1.11.5 Exploratory and Post Hoc Analyses

A small proportion of study participants [51/1602 (3.2%)] had missing or out-of-day range samples/results which caused these participants to be excluded from the primary immunogenicity analysis population.

In order to evaluate the effect of the missing or out of day range sample/results, the Applicant conducted post hoc analyses evaluating an immunogenicity population that consisted of all vaccinated participants with baseline serology data and no major protocol violations. The post hoc analyses were conducted for the primary and key secondary immunogenicity endpoints (e.g., GMT, GMFI,) for both GP-ELISA and PRNT. The results of the post hoc analyses were consistent with the results of the immunogenicity analyses using the PP immunogenicity population.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety was assessed for all vaccinated subjects from baseline through Month 12 postvaccination. At each follow-up visit, participants were asked questions to assess the development of any serious medical conditions (e.g., malaria), the possibility of unreported SAEs, and for women whether they are pregnant. Temperature was recorded, and blood was drawn for immunogenicity testing.

Additional information/specimens were obtained for pediatric participants during the first week (Days 1 through 6) following the first and second vaccination. Study personnel contacted pediatric participants daily to assess injection site reactions, targeted systemic symptoms, SAEs and to measure temperature. All other safety procedures for pediatric participants were conducted during scheduled visits at the same time points as adults (Days 7, Day 14 and 28 postvaccination). Participants were offered antipyretic medication at baseline, and the use (yes/no) of antipyretic medication on the day of vaccination and within 48 hours postvaccination was reported on the CRFs.

At study visits on Days 7, 14, and 28 postvaccination, participants were prompted to report solicited injection-site and solicited systemic AEs of any grade severity and unsolicited Grade 3 or 4 AEs that had occurred since the last study visit. Solicited injection-site AEs and solicited systemic AEs were considered related to the study intervention.

Injection site reactions and symptoms were graded as follows:

- Grade 1 – symptoms causing no or minimal interference with usual social & functional activities
- Grade 2 - symptoms causing greater than minimal interference with usual social & functional activities
- Grade 3 - symptoms causing inability to perform usual social & functional activities; and
- Grade 4 - symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death.

SAEs and EVD were to be assessed and reported on the case report form (CRF) within 24 hours of the investigator's knowledge of the event. Relationship of SAEs were determined by the investigator, by answering the question: "Is there a reasonable possibility that the AE may have been caused by the study product (vaccine)? as a "yes" or "no" response. Malaria events were assessed and reported at each follow-up visit. Malaria events were to be assessed at each follow-up visit (Days 7, 14, 28 and Months 6 and 12) post first vaccination. Laboratory-confirmed malaria events that did not require hospitalization were not considered SAEs.

MedDRA version 22 was used for the assessment of safety.

Laboratory test results were graded for severity according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014. Grade 3 or 4 abnormal clinical laboratory test results were to be considered clinically significant by the investigator. For adult participants, laboratory tests were collected at screening/baseline only. For pediatric participants, laboratory tests were collected at baseline/screening and at Day 7 postvaccination 1 and 2.

Women who reported being pregnant in the first three months of follow-up post first vaccination were followed for the outcome of their pregnancy and the outcome was reported on a CRF. Women who reported being pregnant prior to the second vaccination or who have a positive pregnancy test at 56 days could not receive the second vaccination, however they remained under follow-up. 13 pregnancies that occurred from the first vaccination through the Month 3 visit (Month 1 after second vaccination) were followed for the outcome of their pregnancies. Congenital anomalies or birth defects in the offspring of the study participants were reported as SAEs. Please see Section 9.1.1 for more details on the pregnancy outcomes reported as SAEs.

Unanticipated problems (UPs) that were not related to study vaccines, for examples, a breach of subject confidentiality, were to be reported to the respective Ethical/Institutional Review Committees (IRB) in accordance with the requirements of the committee for oversight of the particular site where the UP occurred. UPs related to the study vaccines were to be reported per AE/SAE reporting requirements.

Reviewer Comment: *FDA concurred with the plan to assess only severe unsolicited events as being most relevant to this vaccine indicated to prevent a life-threatening illness.*

6.1.12.2 Overview of Adverse Events

Table 15 and Table 16 provide an overview of AEs in pediatric and adult participants through Month 12 following vaccination.

Table 15. Adverse Events Through Month 12 (Pediatric Participants)

Event	Ervebo 1 Dose N=410 n (%)	Ervebo 2 Dose N=198 n (%)	Pooled Ervebo[a] N=608 n (%)	Pooled Placebo[b] N=388 n (%)
Solicited AEs through Day 28 post first vaccination	--	--	--	--
≥1 solicited AEs	350 (85.4)	169 (85.4)	519 (85.4)	263 (67.8)
Injection site reactions	191 (46.6)	74 (37.4)	265 (43.6)	51 (13.1)
Systemic AEs	336 (82.0)	162 (81.8)	498 (81.9)	251 (64.7
SAEs through Month 12 postvaccination	--	--	--	--
≥1 SAEs through Month 12	9 (2.2)	3 (1.5)	12 (2.0)	8 (2.1)
Deaths	3 (0.7)	0 (0.0)	3 (0.5)	2 (0.5)

Source: Adapted from sBLA 125690/55; Clinical Study Report Table 12-7, page 191-192
Abbreviations: sBLA=supplemental Biologics License Application; AE=adverse events; SAE=serious adverse event. [a] Pooled Ervebo = Ervebo 1 dose or 2 doses
[b] Pooled placebo = 0.5 and 1.0 mL placebo groups

Table 16. Adverse Events Through Month 12 (Adults)

Event	Ervebo 1 Dose N=405, n (%)	Ervebo 2 Dose N=187, n (%)	Pooled Ervebo[a] N=592, n (%)	Pooled Placebo[b] N=412, n (%)
Solicited AEs through Day 28 post first vaccination	--	--	--	--
≥1 solicited AEs	312 (77.0)	140 (74.9)	452 (76.4)	272 (66.0)
Injection site reactions	106 (26.2)	47 (25.1)	153 (25.8)	37 (9.0)
Systemic AEs	301 (74.3)	137 (73.3)	438 (74.0)	265 (64.3)
SAEs through Month 12 postvaccination	--	--	--	--
≥1 SAEs through Month 12	6 (1.5)	1 (0.5)	7 (1.2)	5 (1.2)
Deaths	3 (0.7)	0 (0.0)	3 (0.5)	1 (0.2)

Source: Adapted from sBLA 125690/55; Clinical Study Report Table 12-9, page 195-196
Abbreviations: sBLA=supplemental Biologics License Application; AE=adverse event; SAE=serious adverse event.
[a] Pooled Ervebo = Ervebo 1 dose or 2 doses
[b] Pooled placebo = 0.5 and 1.0 mL placebo groups

Reviewer Comment: *As seen in Table 15 and Table 16 above, the proportion of pediatric participants who experienced one or more AEs in the pooled Ervebo group post first vaccination was higher (85.4%) than in adult participants (76.4%). This was mainly due to a higher percentage of injection-site reactions in pediatric participants (43.6% - see Table 18 below) than in adult participants (25.8% - see Table 19 below). The proportion of participants with systemic and nonserious AEs was also higher in pediatric participants (81.9%) than adult participants (74%). The AE profiles for pediatric and adult participants in the 2-dose Ervebo group post second vaccination were generally comparable*.

Solicited Injection Site Reactions Through Day 28 Post First Vaccination

Table 17 through Table 19 provide an overview of injection site reactions in pediatric participants and adults through Day 28 post first vaccination.

Table 17. Solicited Injection Site Reactions Through Day 28 Post First Vaccination (Pediatric Participants)

Preferred Term	Pooled Ervebo[a] N=608 n (%)	Pooled Placebo[b] N=388 n (%)
Injection site reactions	265 (43.6)	51 (13.1)
Injection site pain	253 (41.6)	44 (11.3)
Injection site swelling	18 (3.0)	9 (2.3)
Injection site pruritis	25 (4.1)	1 (0.3)
Injection site erythema	3 (0.5)	3 (0.8)

Source: Adapted from sBLA 125690/55; Clinical Study Report Table 12-7, page 191-192
Abbreviations: sBLA=supplemental Biologics License Application.
[a] Pooled Ervebo = Ervebo 1 dose or 2 doses
[b] Pooled placebo = 0.5 and 1.0 mL placebo groups

The table below summarizes solicited injection site reactions from Day 1 through Day 28 post first vaccination in pediatric participants.

Table 18. Solicited Injection Site Reactions Through Day 28 Post First Vaccination (Pediatric Participants by Age Subgroup)

Preferred Term	<3 years old N = 95, n (%)	3-11 years old N = 310, n (%)	12-17 years old N = 203, n, (%)
Injection site reactions	29 (30.5)	128 (41.3)	108 (53.2)
Injection site pain	25 (26.3)	122 (39.4)	106 (52.2)
Injection site swelling	5 (5.3)	8 (2.6)	5 (2.5)
Injection site pruritis	0 (0.0)	20 (6.5)	5 (2.5)
Injection site erythema	1 (1.1)	1 (0.3)	1 (0.5)

Source: Adapted from sBLA 125690/55; Clinical Study Report Table 14.3-49, 50 and 51, pages 678-683
Abbreviations: sBLA=supplemental Biologics License Application

The table below is a description of the solicited injection site reaction from Day 1 through Day 28 post first vaccination in adults.

Table 19. Injection Site Reactions Through Day 28 Post First Vaccination (Adult Participants)

Preferred Term	Pooled Ervebo[a] N=592 n (%)	Pooled Placebo[b] N=412 n (%)
Injection site reactions	153 (25.8)	37 (9.0)
Injection site pain	127 (21.5)	17 (4.1)
Injection site swelling	22 (3.7)	12 (2.9)
Injection site pruritis	13 (2.2)	6 (1.5)
Injection site erythema	8 (1.4)	10 (2.4)

Source: Adapted from sBLA 125690/55; Clinical Study Report Table 12-9, page 195-196
Abbreviations: sBLA=supplemental Biologics License Application.
[a] Pooled Ervebo = Ervebo 1 dose or 2 doses
[b] Pooled placebo = 0.5 and 1.0 mL placebo groups;

Through Day 28 post first vaccination, higher proportions of injection site reactions were reported in the pooled Ervebo group compared to the placebo group among both pediatric (43.6% vs. 13.1%) and adult (25.8% vs. 9%) participants.

Injection site pain was the most commonly reported injection site reaction, and it was reported in 41.6% (253/608) of pediatric participants compared to 21.5% (127/592) of adult participants in the pooled Ervebo group through Day 28 post first vaccination.

In the pediatric age subgroups, injection site pain was more common in the 12-17 years age group at 52.2% (106/203), compared to the 3-11 years age group at 39.4% (122/310) and the 12 months through 3 years age group at 26.3% (25/95).

Most events of the injection site pain were reported in the first seven days post vaccination and were more frequent among both pediatric participants (18.4%; 112/608) and adult participants (18%; 73/405) who received Ervebo than among placebo recipients in the pediatric (3.4%; 13/388) and adult (3.2%; 13/412) age groups. All the reported injection site reactions were mild or moderate, and there were no ≥ Grade 3 solicited events in participants who received Ervebo.

Solicited systemic AEs through Day 28 Post First Vaccination

The following tables (Table 20 through Table 22) summarize solicited systemic events in pediatric and adult participants through Day 28 post first vaccination.

Table 20. Solicited Systemic AES Through Day 28 Postvaccination (Pediatric Participants)

Event	Pooled Ervebo[a] N=608 n (%)	Pooled Placebo[b] N=388 n (%)
Solicited systemic AEs	498 (81.9)	251 (64.7)
Feverishness	378 (62.2)	150 (38.7)
Headache	278 (45.7)	122 (31.4)
Somnolence[†]	143 (23.5)	49 (12.6)
Decreased appetite	142 (23.4)	54 (13.9)
Abdominal pain	99 (16.3)	47 (12.1)
Myalgia	96 (15.8)	20 (5.2)
Chills	88 (14.5)	44 (11.3)
Dizziness	60 (9.9)	23 (5.9)
Vomiting	58 (9.5)	28 (7.2)
Nausea	43 (7.1)	18 (4.6)
Arthralgia	42 (6.9)	14 (3.6)
Crying	39 (6.4)	9 (2.3)
Diarrhea	35 (5.8)	24 (6.2)
Skin lesion	30 (4.9)	32 (8.2)
Abnormal sweating	16 (2.6)	7 (1.8)
Mouth ulceration	15 (2.5)	2 (0.5)
Irritability	13 (2.1)	1 (0.3)
Screaming	11 (1.8)	2 (0.5)
Joint swelling	3 (0.5)	2 (0.5)

Source: Adapted from sBLA 125690/55; Clinical Study Report Table 12-7, page 191-192
Abbreviations: sBLA=supplemental Biologics License Application; AE=adverse event
[†] Includes: somnolence, reduced activity and fatigue.
[a] Pooled Ervebo = Ervebo 1 dose or 2 doses
[b] Pooled placebo = 0.5 and 1.0 mL placebo groups

Solicited systemic AEs through Day 28 post first vaccination in pediatric participants by age subgroup is described in Table 21 below.

Table 21. Solicited Systemic AEs Through Day 28 Postvaccination (Pediatric Participants by Age Subgroups)

Event	< 3 years old N = 95 n (%)	3 – 11 years old N = 310 n (%)	12 – 17 years old N = 154 n (%)
Solicited systemic AEs	83 (87.4)	128 (41.3)	154 (75.9)
Feverishness	79 (83.2)	204 (64.8)	98 (48.3)
Headache	4 (4.2)	154 (49.7)	120 (59.1)
Somnolence	19 (20.0)	67 (21.6)	57 (28.1)
Decreased appetite	26 (27.4)	74 (23.9)	42 (20.7)
Abdominal pain	2 (2.1)	65 (21.0)	32 (15.8)
Myalgia	0 (0.0)	36 (11.6)	60 (29.6)
Chills	5 (5.3)	44 (14.2)	39 (19.2)
Dizziness	0 (0.0)	26 (8.4)	34 (16.7)
Vomiting	16 (16.8)	34 (11.0)	8 (3.9)
Nausea	0 (0.0)	26 (8.4)	17 (8.4)
Arthralgia	0 (0.0)	10 (3.2)	32 (15.8)
Crying	29 (30.5)	10 (3.2)	0 (0.0)
Diarrhea	18 (18.9)	9 (2.9)	8 (3.9)
Skin lesion	9 (9.5)	18 (5.8)	3 (1.5)
Abnormal sweating	2 (2.1)	4 (1.3)	10 (4.9)
Mouth ulceration	6 (6.3)	6 (1.9)	3 (1.5)
Irritability	10 (10.5)	3 (1.0)	0 (0.0)
Screaming	9 (9.5)	2 (0.6)	0 (0.0)
Joint swelling	0 (0.0)	1 (0.3)	2 (1.0)

Source: Adapted from sBLA 125690/55; Clinical Study Report Table 14.3-49, 50 and 51, pages 678-683
Abbreviations: sBLA=supplemental Biologics License Application

Solicited systemic AEs through Day 28 post first vaccination in adults are described in Table 22 below.

Table 22. Solicited Systemic AEs Through Day 28 Post First Vaccination (Adults)

Event	Pooled Ervebo[a] N=592 n (%)	Pooled Placebo[b] N=412 n (%)
Solicited systemic AEs	438 (74.0)	265 (64.3)
Headache	326 (55.1)	179 (43.4)
Feverishness	232 (39.2)	94 (22.8)
Myalgia	175 (29.6)	65 (15.8)
Somnolence	151 (25.5)	56 (13.6)
Arthralgia	110 (18.6)	44 (10.7)
Chills	99 (16.7)	35 (8.5)
Decreased appetite	90 (15.2)	39 (9.5)
Abdominal pain	77 (13.0)	46 (11.2)
Dizziness	58 (9.8)	34 (8.3)
Nausea	56 (9.5)	26 (6.3)
Vomiting	26 (4.4)	5 (1.2)
Diarrhea	20 (3.4)	14 (3.4)
Skin lesion	15 (2.5)	10 (2.4)
Mouth ulceration	13 (2.2)	2 (0.5)

Event	Pooled Ervebo[a] N=592 n (%)	Pooled Placebo[b] N=412 n (%)
Abnormal sweating	8 (1.4)	4 (1.0)
Joint swelling	4 (0.7)	0 (0.0)

Source: Adapted from sBLA 125690/55; Clinical Study Report Table 12-9, page 195-196
Abbreviations: sBLA=supplemental Biologics License Application; AE=adverse event.
[a] Pooled Ervebo = Ervebo 1 dose or 2 doses
[b] Pooled placebo = 0.5 and 1.0 mL placebo groups

Solicited systemic AEs through Day 28 post first vaccination were more frequent in the pooled Ervebo group compared to the placebo group for both the pediatric (81.9% vs. 64.7%, respectively) and adult (74% vs. 64.3%, respectively) participants.

As seen in the tables above, the most commonly (>20%) reported solicited systemic AEs were feverishness, headache, somnolence, and decreased appetite. For the individual events, the proportion of participants were comparable across intervention groups, with the exception of feverishness, headache, somnolence, and myalgia, which were reported at a higher incidence in the Ervebo groups compared to placebo.

Overall, the solicited systemic AEs were reported most frequently at the Day 7 visit in the pooled Ervebo group (62.0%) compared to the placebo group (42.3%). At the Day 28 visit post first vaccination, the proportion of participants with ≥1 solicited systemic AEs was comparable in the pooled Ervebo group (22.8%; 274/1200) and the placebo group (24.4%; 195/800).

Feverishness was the most commonly reported solicited systemic AE in pediatric participants, occurring in 83.2% (79/95) of participants 12 months through 3 years of age compared to 64.8% (204/310) of participants 3-11 years of age and 48.3% (98/203) of participants 12-17 years of age.

Reviewer Comment: *To determine AEs of pyrexia, participants were queried regarding feverishness since their last visit (solicited AE). Feverishness was the most common solicited systemic AE in the overall population and had the highest reported rates in participants 12 months through 3 years of age.*

Most solicited AEs were reported with a toxicity grade of Grade 1 or Grade 2. Grade 3 solicited systemic AEs were reported in 6 participants (4 pediatric and 2 adult) post first vaccination. The four Grade 3 solicited systemic events that occurred in 2 pediatric participants in the 1-dose Ervebo group (1 child with fatigue, chills, decreased appetite and headache and 1 child with fatigue), and 2 participants in the 2-dose Ervebo group (1 child with fatigue and 1 child with pyrexia). The two Grade 3 solicited systemic AEs that occurred in adults were headache in 1 participant (1-dose Ervebo group) and diarrhea in 1 participant (placebo group). None of the Grade 3 systemic AEs were considered to be related to Ervebo.

Maximum temperatures through Day 28 post first vaccination
A maximum temperature of ≥38.0 °C (100.4°F) was reported in 28.1% of pediatric participants compared to 5.2% in adult participants post first vaccination. In the pooled Ervebo group of pediatric participants, maximum body temperature ≥38.0°C post the first vaccination was reported in 25.2% of those who took an antipyretic and 33.8% of those that did not take an antipyretic.

Maximum temperature >40.0°C was not observed in any pediatric age group where antipyretic was not administered. However, maximum temperature >40.0°C was observed in three participants in the 12 – 17-year age group, and one participant in the 3 – 11-year age group for the pooled Ervebo group compared to none in the placebo group.

On May 4, 2023, an information request was sent to the Applicant requesting a review of the postvaccination temperature tables included in the CSR and mapping of data capturing antipyretic use within 48 hours postvaccination.

The Applicant responded on May 25 after reverifying the data mapped to the immunogenicity and safety dataset as presented in the CSR. In the Applicant's response, the investigation of postvaccination temperatures and data capturing antipyretic use within 48 hours postvaccination confirmed the following:

- Pre-vaccination Day 0 temperatures were included in the postvaccination temperatures included in the CSR. The Day 0 temperature measurement was used to confirm conformance with inclusion/exclusion criteria at the time of enrollment/randomization and should not have been included in the dataset that captures postvaccination temperature. The Applicant subsequently provided corrected tables that excluded Day 0 temperatures.

- All temperatures collected and reported on the CRFs in the PREVAC study were temporal measurements, before converting to oral equivalents. The temporal temperatures collected from those eligible for enrollment on Day 0 pre-vaccination were <38°C and consistent with the inclusion/exclusion criteria for the study. Day 0 (pre-vaccination) temperatures >38°C that represented oral equivalent after conversion from temporal temperatures were found during further analysis by the Applicant. The Applicant then presented a corrected CSR table with only unconverted temporal measurements.

- An overestimate of the postvaccination temperatures was initially presented in the CSR due to misinterpretation of antipyretics distribution on Day 0 (for future use) for antipyretic administration 48 hours postvaccination. 163 pediatric participants (n= 51 participants in the Ervebo group, n=112 participants in the placebo group) who were not administered antipyretics postvaccination were reported as having been administered antipyretics postvaccination. The Applicant reported that the errors in the data was not due to a systemic mapping issue, but rather due to secondary interpretations of the CRFs which was corrected in updated tables.

In their response, the Applicant provided a table that presented maximum temperatures (temporal) from Day 1 to Day 7 postvaccination by age group for the pediatric participants enrolled under protocol version 4 as seen in the table below.

Table 23: Percentage of Participants 12 Months Through 17 Years of Age with Fever[a] Within 7 Days Post First Vaccination

Age	Maximum Temperature (Temporal)	Pooled Ervebo[a] %	Pooled Placebo[b] %
12 Months through 2 Years of Age		**N=95**	**N=60**
	≥38.0°C to ≤38.4°C	3.2	1.7
	>38.4°C to ≤38.9°C	3.2	1.7
	>38.9°C to ≤40.0°C	0.0	1.7
	>40.0°C	0.0	0.0
3 Years through 11 Years of Age		**N=310**	**N=205**
	≥38.0°C to ≤38.4°C	4.2	0.5
	>38.4°C to ≤38.9°C	1.0	1.5
	>38.9°C to ≤40.0°C	1.3	0.0
	>40.0°C	0.0	0.0
12 Years through 17 Years of Age		**N=203**	**N=122**
	≥38.0°C to ≤38.4°C	2.5	0.8
	>38.4°C to ≤38.9°C	2.5	0.8
	>38.9°C to ≤40.0°C	2.5	0.8
	>40.0°C	0.0	0.0

Source: Clinical Information Amendment Response, STN 125690.55 (amend 17), page 24 and draft labeling (amend 18), page 7
[a] The use of antipyretic medication within 48 hours postvaccination was reported in 67% and 43% of participants 12 months through 2 years of age, 58% and 37% of participants 3 through 11 years of age, and 52% and 27% of participants 12 through 17 years of age for Ervebo and placebo, respectively.
[a] Pooled Ervebo = Ervebo 1 dose or 2 doses
[b] Pooled placebo = 0.5 and 1.0 mL placebo groups

Reviewer Comment: *Daily temperature outside of scheduled visits were not recorded. Postvaccination temperature measurements were collected on Days 1-6 for pediatric participants and at study visits for all study participants. Therefore, temperature measurements are unlikely representative of the true rate of fever, which would mainly be expected to occur within the first week postvaccination. The corrected postvaccination data presented in the IR from the Applicant showed a higher rate of postvaccination temperatures in the Ervebo groups compared to placebo. Overall, the maximum temperature reported in the corrected data is slightly lower than the prior presentation, but with a similar pattern across age groups. Therefore, the corrected data did not change the risk benefit ratio of the Ervebo vaccination in pediatric participants.*

Unsolicited Adverse Events

Only Grade 3 and 4 unsolicited AEs were reported on the CRFs in this study. The table below summarizes four participants (two children and two adults) who reported a Grade 3 and 4 unsolicited AE during the study:

Table 24: Unsolicited Adverse Events Postvaccination 1 Through Month 12

Age (Years)	Regimen	Adverse Event	# Day Post First Vaccination	Grade	Severity
6	Ervebo – 2 doses	Insomnia	8	3	Severe
17	Ervebo – 2 doses	Blindness, unilateral	29	4	Severe
38	Ervebo – I dose	Hypertension	22	3	Severe
40	Placebo – 2 doses	Toothache	64	3	Severe

Source: Adapted from STN 125690 CSR

Below is the narrative on the patient with unilateral blindness:

- A 17-year-old-male (Ervebo/Ervebo) with history of conjunctivitis and "watering of both eyes periodically" with reported history of total vision loss of the right eye that started with blurry vision in the right eye on Day 29 post first vaccination. He proceeded to wash his eyes with "some concoction made of leaves and tamarind", followed by expired antibiotic eye drops with gentamicin as the main component, resulting in the complete loss of vision in the right eye the following day, per report. The patient evaluated by an ophthalmologist 5 days after initial presentation and was diagnosed with unilateral optic neuropathy of the right eye and started on prednisolone with some improvement in vision that was not back to baseline.

Reviewer Comment: *The rates of the unsolicited AEs in this study were low. In the 12 months post first vaccination, severe unsolicited events were reported in four participants. None of the four unsolicited AEs were considered related by the investigator. The Grade 3 AEs were not uncommon medical events, nor did they present in a manner or pattern suggesting a safety concern. The event of Grade 4 unilateral blindness was temporally related; however, the use of a concoction and expired gentamicin are plausible alternative etiologies that may have contributed to the event. Additionally, despite the temporal relationship to vaccine, the participant went on to receive the second dose of vaccine without exacerbation or worsening of the condition. Although the case information is limited, to determine causality, but given other plausible causes/aggravating factors, vaccine relatedness seems unlikely.*

6.1.12.3 Deaths

As shown in Table 25 below, a total of 9 vaccinated participants (5 pediatric and 4 adult) reported 9 SAEs with a fatal outcome under protocol version 4.0.

Table 25. Deaths Through Month 12, Protocol Version 4.0

Age (Years)	Regimen	Adverse Event	# Days Post First Vaccination	#Days from Last Vaccination	Alternative Plausible Etiology
4	Ervebo 1-dose	Death*	(b) (6)		Fever or undetermined origin
5	Ervebo 1-dose	Drowning			N/A
13	Ervebo 1-dose	Death*			Acute symptoms of dizziness and fainting
13	Placebo 1-dose	Death*			Suspected meningitis
16	Placebo 2-dose	Sickle cell anemia with crisis			Malaria
18	Ervebo 1-dose	Sepsis			Skin and soft tissue infection of the LLE
33	Ervebo 1-dose	HIV infection			Malaria
36	Ervebo 1-dose	Appendectomy			Appendicitis Pulmonary TB Malaria Ill-defined disorder
73	Placebo 2-dose	Anemia			Malaria

Source: Adapted from sBLA 125690/55; Clinical Study Report Table (Page 200) and Patient Narratives
Abbreviation: sBLA=supplemental Biologics License Application

None of the deaths were considered to be related to the study vaccination by the investigator. Applicant and the FDA agreed with the investigator's assessment.

Narratives of the events reported post Ervebo and placebo without a clear etiology for the fatal outcome included the following:

- A 4-year-old female (Ervebo/placebo boost) was reported to have fever on Day 163 postvaccination 1 and died at home on Day (b) (6) postvaccination 1 with no additional information reported. The primary cause of death was pyrexia.
- A 13-year-old male (Ervebo/placebo boost) reported fainting and dizziness on Day (b) (6) postvaccination 1 at a healthcare center. The on-call physician decided to refer patient to a higher level of care. However, he died before the referral form was completed. The primary cause of death was unknown.
- A 13-year-old male (placebo/placebo boost) reported fever and altered consciousness on Day 49 postvaccination 1. Meningitis was suspected and diagnostic tests including cerebrospinal fluid analysis were performed. However, the participant died on Day (b) (6) postvaccination before results were available following complications of the suspected meningitis. The primary cause of death was unknown.

Reviewer Comment: *Nine deaths were reported in six participants (3 pediatrics, 3 adult) in the 1-dose Ervebo group and three participants (2 pediatric, 1 adult) in the placebo group. The deaths occurred between 51 -373 days postvaccination 1 and 21-317 days post last vaccination. No deaths were reported in pediatric participants younger than 3 years old. All of the fatal SAEs were unsolicited events.*

The primary cause of death was unknown for three pediatric participants (two in the 1-dose Ervebo arm and the other in the placebo arm). The narratives provided for these three pediatric participants showed they died soon after presentation to a healthcare provider, before the cause of death could be established. There is limited information available for the fatal events due to unknown causes, which precludes a full assessment of causality. No clear temporal relationship to vaccination and death due to unknown causes was established in participants in the Ervebo and placebo groups. These participants did not experience any vaccine-related non-serious AEs at any point during the study.

None of the other deaths in pediatric participants and adults were considered related to the study vaccination based on the investigator's assessment and clinical review of the participant narratives. No clear pattern of events or biologically plausible mechanism to suggest causality to vaccine is evident from the available information.

6.1.12.4 Nonfatal Serious Adverse Events

Under protocol version 4.0 of Study V920-016, a total of 44 SAEs were reported by 32 (12 adults, 20 pediatric) participants from the first vaccination to the end of the base study (Month 12) as seen in the table below.

Table 26 below summarizes the SAEs that were reported in the adult and pediatric participants through Month 12 of the study.

Table 26. Participants With SAEs From First Vaccination Through Month 12

Ervebo	Ervebo 1 Dose	Ervebo 2 Dose	Pooled Ervebo[a]	Pooled Placebo[b]
Adults	**N = 405 n (%)**	**N = 187 n (%)**	**N = 592 n (%)**	**N = 412 n (%)**
Subjects ≥ 1 SAEs	6 (1.5)	1 (0.5)	7 (1.2)	5 (1.2)
Pediatrics	**N = 410 n (%)**	**N = 198 n (%)**	**N = 608 n (%)**	**N = 388 n (%)**
Subjects ≥ 1 SAEs	9 (2.2)	3 (1.5)	12 (2.0)	8 (2.1)

Source: Adapted from sBLA 125690/55; Clinical Study Report Table 12-11, page 203-205.
Abbreviations: sBLA=supplemental Biologics License Application; SAE=serious adverse event.
[a] Pooled Ervebo = Ervebo 1 dose or 2 doses
[b] Pooled placebo = 0.5 and 1.0 mL placebo groups

Table 27 and Table 28 below summarize the nonfatal SAEs that were reported in adult and pediatric participants through Month 12 of the study.

Table 27: Adult Participants[a] with Non-fatal SAEs from First Vaccination Through Month 12

System Organ Class Preferred Term	Ervebo 1 Dose	Ervebo 2 Dose	Pooled Ervebo[b]	Pooled Placebo[c]
Adults	**N = 405 %**	**N = 187 %**	**N = 592 %**	**N = 412 %**
≥ 1 Nonfatal SAEs	**1.2**	**0.5**	**1.0**	**1.0**
Gastrointestinal disorders	**0.2**	**0**	**0.2**	**0**
Abdominal pain upper	0.2	0	0.2	0
General disorders and administration site conditions	**0.2**	**0**	**0.2**	**0**
Ill-defined disorder	0.2	0	0.2	0
Infections and infestations	**0.5**	**0.5**	**0.7**	**0.7**
Appendicitis	0.2	0.5	0.2	0.5
Cellulitis	0	0	0	0.2
Peritonitis	0.2	0	0.2	0
Injury, poisoning and procedural complications	**0.2**	**0**	**0.2**	**0.2**
Head injury	0	0	0	0.2
Humerus fracture	0.2	0	0.2	0
Pregnancy, puerperium and perinatal conditions	**0.2**	**0**	**0.2**	**0**
Ectopic pregnancy	0.2	0	0.2	0

Source: STN 125690 CSR, page 203-207
[a] Every participant is counted a single time for each applicable row and column.
[b] Pooled Ervebo = Ervebo 1 dose or 2 doses
[c] Pooled placebo = 0.5 and 1.0 mL placebo groups

Table 28. Pediatric Participants[a] with Non-fatal SAEs from First Vaccination Through Month 12

System Organ Class Preferred Term	Ervebo 1 Dose	Ervebo 2 Dose	Pooled Ervebo[b]	Pooled Placebo[c]
Pediatrics	**N = 410 %**	**N = 198 %**	**N = 608 %**	**N = 388 %**
≥ 1 Nonfatal SAEs	**1.7**	**3.5**	**2.0**	**1.8**
Eye disorders	**0**	**0.5**	**0.2**	**0**
Optic neuropathy/ Blindness (unilateral)	0	0.5	0.2	0

System Organ Class Preferred Term	Ervebo 1 Dose	Ervebo 2 Dose	Pooled Ervebo[b]	Pooled Placebo[c]
Pediatrics	**N = 410 %**	**N = 198 %**	**N = 608 %**	**N = 388 %**
Gastrointestinal disorders	**0.5**	**0**	**0.3**	**0**
Acute abdomen	0.2	0	0.2	0
Hemoperitoneum	0.2	0	0.2	0
General disorders and administration site conditions	**0.2**	**0.5**	**0.3**	**0**
Ill-defined disorder	0	0.5	0.2	0
Pyrexia	0.2	0	0.2	0
Infections and infestations	**0.2**	**0.5**	**0.7**	**1.0**
Appendicitis	0.2	0	0.2	0.5
Malaria	0	0.5	0.2	0.3
Pneumonia	0	0	0	0.3
Typhoid fever	0.2	0	0.2	0
Injury, poisoning and procedural complications	**0.2**	**1.5**	**0.7**	**0.5**
Capsular block syndrome	0.2	0	0.2	0
Clavicle fracture	0	0	0	0.3
Eye injury	0	0.5	0.2	0
Humerus fracture	0	0.5	0.2	0
Radius fracture	0	0.5	0.2	0
Venom poisoning	0	0	0	0.3
Musculoskeletal and connective tissue disorders	**0.2**	**0**	**0.2**	**0**
Back pain	0.2	0	0.2	0
Pregnancy, puerperium and perinatal conditions	**0.2**	**0**	**0.2**	**0**
Abortion incomplete	0.2	0	0.2	0

Source: STN 125690 CSR, page 203-207
[a] Every participant is counted a single time for each applicable row and column.
[b] Pooled Ervebo = Ervebo 1 dose or 2 doses
[c] Pooled placebo = 0.5 and 1.0 mL placebo groups

A combination of AEs were encoded by the preferred term of “ill-defined disorder”.
One adult participant in the Ervebo 1-dose group experienced a pregnancy SAE of “ill-defined disorder (please see Section 9.1.1 for further details) and one pediatric participant in the Ervebo 2-dose group experienced an “ill-defined disorder”, the details of which are described below:

- A 5-year-old female (Ervebo/Ervebo boost) was hospitalized for malaria, anemia (hemoglobin (Hb) was 4 g/dl), prostration and hypoglycemia on day 42 postvaccination 1. The participant was transfused and treated with artesunate, paracetamol, ceftriaxone, glucose, and iron and discharged on an unknown date. On day 58 postvaccination 1, her Hb was 11.1 g/dl, and a second Ervebo vaccination was administered. The investigator did not consider the events of malaria, anemia, hypoglycemia, and radius fracture to be

related to the study vaccination. There was no evidence to suggest a causal relationship between the vaccination and the reported SAEs.

No SAEs were reported in subjects >65-year-old.

Reviewer Comment: *The proportion of participants who reported one or more SAE postvaccination 1 through Month 12 was low overall and similar across treatment groups with slightly higher rates in the pediatric (1.8 – 2.0%) vs adult participants (1.0%).*

The SAEs reported for pediatric participants and adults post dose 1 through Month 12 mainly occurred in n = 1 participant, with the exception of appendicitis (n = 3), malaria (n=2), and ill-defined disorder (n = 3). Overall, no emergent pattern of SAEs was seen.

The causality assessment provided by the investigator appears appropriate for the non-fatal SAEs. The time to onset of non-fatal SAEs in participants in the Ervebo group occurred >30 days postvaccination 1. No clear pattern of events or biologically plausible mechanism to suggest causality from the available information.

6.1.12.5 Adverse Events of Special Interest (AESI)

Ebola Virus Disease (EVD) Events

According to the protocol, EVD events were to be recorded on the CRF within 24 hours of the site's personnel's knowledge of the event, and a sample of blood was to be stored for future research. No EVD event was reported through Month 12.

Malaria Events

Malaria events were to be assessed at each follow-up visit. Malaria events that met the SAE definition were reported on the SAE form. Two pediatric participants had laboratory-confirmed malaria that required hospitalization, one in the 2-dose Ervebo group and one in the placebo group. The reported malaria in the 2-dose Ervebo group occurred in a 5-year female participant on day 41 postvaccination 1. The event was not considered to be related to the study vaccination by the investigator.

Reviewer Comment: *No evidence to suggest causality between the malaria event and Ervebo vaccination based on the available information.*

Unanticipated Problems (UP) Events

Appendicitis was the most frequently reported SAE in the PREVAC study. Nine events of appendicitis reported under protocol version 4 occurred in participants aged 10 – 39 years old. Eight of the events occurred in Guinea, and one in Liberia. The high incidence of appendicitis met the protocol definition of UP, prompting an investigation into the cause.

No observed differences were observed in the incidence of appendicitis among the Ervebo and placebo groups based on the investigation conducted by the Applicant. Following the investigation, the Guinean investigators received additional medical training to reinforce their knowledge of appendicitis and appropriate documentation of new cases. The study benefit/risk ratio was not modified due to this unanticipated problem, and the study was allowed to proceed. The number of participants with appendicitis were also reported to have decreased after the training.

Reviewer Comment: *In the PREVAC study, 20 events of appendicitis were reported under protocol version 3 (11 events) and protocol version 4 (9 events). Pediatric participants in the 12-17 year age group reported 12 events of appendicitis and 8 events were reported in adult participants 18 – 65 years old. No events of appendicitis were reported in pediatric participants < 3 years old and adults >65 years old.*

While a higher frequency of appendicitis was reported in the PREVAC study, the age distribution of appendicitis reported in the study was consistent with the general population, with highest incidence of appendicitis found in participants aged 10 to 19 years, and lower incidence in extreme age groups of very young or old. Available information does not indicate a clear pattern of vaccine associated appendicitis events or a biologically plausible mechanism to suggest vaccine causality.

6.1.12.6 Clinical Test Results

Routine laboratory testing was obtained at baseline for all participants. Additional laboratory testing was performed on Day 7 following vaccination 1 and 2 in the pediatric participants. No reported additional laboratory testing due to the occurrence of AEs was performed.

Reviewer Comment: *No clinically significant changes in hematology or serum chemistry were observed for pediatric participants in any of the study intervention groups (data not shown) .*

Ervebo Shedding in Pediatric Participants

A saliva sample sub study of viral shedding was conducted in Guinea to estimate the proportion of pediatric participants with detectable vaccine virus by reverse transcriptase polymerase chain reaction (PCR) and to quantify vaccine virus levels shed after a prime and boost vaccine dose.

Viral shedding was assessed in saliva sample from a subset of 60 pediatric participants at baseline, Days 7, 14, 28, 56, 63, and Month 3. Overall, viral shedding occurred in 31.7% of pediatric participants in the pooled Ervebo group (1-dose Ervebo: 28.2%, 2-dose Ervebo: 38.1%) compared to 0% in the placebo group at any time postvaccination (Table).

Table 2929. Shedding of Ervebo in Pediatric Participants Over Time, Protocol Version 4.0

Assay Time Point	Ervebo 1-Dose N=39 %	Ervebo 2-Dose N=21 %	Pooled Ervebo[a] N=60 %	Pooled Placebo[b] N=36 %
Any time point	28.2	38.1	31.7	0.0
Day 0	2.6	0.0	1.7	0.0
Day 7	23.1	28.6	25	0.0
Day 14	13.2	14.3	13.6	0.0
Day 28	2.6	0.0	1.7	0.0
Day 56	0.0	0.0	0.0	0.0
Day 63	0.0	0.0	0.0	0.0
Month 3	0.0	0.0	0.0	0.0

Source: Adapted from sBLA 125690/55; Clinical Study Report Table 12-13, page 210.
Abbreviations: sBLA=supplemental Biologics License Application; CI=confidence interval; N=number of participants with serology data at one or more timepoints according to the vaccine they were randomized; n=number of participants contributing to the analysis. m=number of participants with shedding.
[a] Pooled Ervebo = Ervebo 1 dose or 2 doses
[b] Pooled placebo = 0.5 and 1.0 mL placebo groups

Viral shedding was greatest on day 7 post dose-1 and declined thereafter, with no shedding detected in any Ervebo group beyond Day 28 including in the 2-Dose group post dose-2.

The results observed for pediatric participants 3 to 11 and 12 to 17 years of age were comparable with those observed for pediatric participants overall. No shedding was detected at any time point in pediatric participants younger than 3 years of age.

Reviewer Comment: *On February 14, 2023, the Applicant submitted a clinical information amendment that updated the number of pediatric participants who shed vaccine virus post first vaccination to include one additional participant (12-year-old female) that was previously unaccounted for. The Ervebo 1-dose and pooled Ervebo dose groups increased from 10/39 (25.6%) to 11/39 (28.2%) and 18/60 (30%) to 19/60 (31.7%), respectively. The addition of this one participant did not impact the overall conclusions of the study.*

6.1.12.7 Dropouts and/or Discontinuations

No participant discontinued from the study due to an AE. Greater than 95% of the randomized participants completed the study received the two assigned vaccinations.

6.1.13 Study Summary and Conclusions

V920-016 was a Phase 2, randomized, double-blind, placebo-controlled study evaluating the safety and immunogenicity of Ervebo in pediatric participants 12 months through 17 years of age in comparison to adult participants 18 years of age and older. Postvaccination GMTs of Zaire ebolavirus (Kikwit) GP-ELISA at Day 28 following vaccination were non-inferior in the pediatric participants as compared to the adult participants meeting the primary immunogenicity endpoint of the study. The vaccine was also generally well tolerated in the pediatric population as compared to the adult population with solicited injection-site reactions, headache, and pyrexia being the the most commonly reported postvaccination events. The proportion of participants reporting unsolicited events, SAEs and deaths were generally low with similar frequency in adults and pediatric participants. No specific event or pattern of events suggested a vaccine safety signal.

7. INTEGRATED OVERVIEW OF EFFICACY

Not applicable. The submission consisted of a single study.

8. INTEGRATED OVERVIEW OF SAFETY

Not applicable. The submission consisted of a single study.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Pregnancy

According to the V920-016 protocol, women who reported being pregnant in the first 3 months of follow-up postvaccination were followed for the outcome of their pregnancy. Testing for pregnancy was required during screening, and pregnant women were excluded from the study.

Ten pregnancies were reported from first vaccination through Month 3 under protocol version 4. Table below summarizes reported pregnancies and their outcomes in the Ervebo 1-dose and placebo groups. No pregnancies were reported in the Ervebo 2-dose groups.

Table 30. Pregnancies and Outcomes Reported Through Month 3 Postvaccination 1

Study Group	Outcome	Day Postvaccination 1 Pregnancy Discovered
Ervebo 1 - dose	Live birth	56
Ervebo 1 - dose	Induced abortion	57
Placebo	Live birth	57
Placebo	Live birth	57
Placebo	Live birth	57
Placebo	Induced abortion	57
Placebo	Induced abortion	57
Placebo	Induced abortion	57
Placebo	Induced abortion	93
Placebo	Not reported	Not reported

Source: FDA-generated table

Reviewer Comment: *Pregnancies with relationship to timing of vaccine reported occurred >30 days post vaccination and the majority of pregnancies occurred in the placebo group. No congenital abnormalities or birth defects were reported.*

Two participants in the Ervebo 1-dose group and four participants in the placebo groups reported pregnancy related SAEs.

Details on the two pregnancy-related SAEs in the Ervebo 1-dose group are as follows:

- A 15-year-old female reported a three-day history of abdominal pain and metrorrhagia after ingesting a cloth-dying product on Day 181 postvaccination. She was transferred to a health facility due to incomplete abortion and an intrauterine aspiration was performed, followed with ambulatory care. The event was considered not to be related to the study vaccination.
- A 27-year-old female was reported to have experienced acute lower abdominal pain on Day 205 postvaccination 1 and diagnosed with ectopic pregnancy. A salpingectomy was performed on Day 206 postvaccination 1. The participant was diagnosed with upper abdominal pain and ill-defined disorder (reported as right polycystic ovarian and appendicitis) on Day 323, and the events were considered resolved on Day 335 postvaccination 1. The investigator did not consider the events to be related to the study vaccination.

Details of pregnancy related SAEs in participants who received placebo are as follows:

- A 16-year-old female was determined to be pregnant on Day 57 postvaccination 1. On Day 283 postvaccination 1, the participant was diagnosed with an ill-defined disorder (reported as second-degree contracted pelvis and acute fetal distress). An emergency cesarean section resulting in a live birth was performed on the same day. The investigator did not consider the event to be related to the study vaccination.
- A 17-year-old female was determined to be pregnant on Day 57 postvaccination 1. The participant had several injections of progesterone + estrone on Day 76 postvaccination 1 and experienced intermenstrual bleeding on Day 87 postvaccination 1. A manual intrauterine aspiration was performed the same day, and the pregnancy resulted in an induced abortion. On Day 94 postvaccination 1, an ultrasound showed trophoblastic

debris following incomplete abortion. A uterine dilatation and evacuation were performed on Day 98 postvaccination 1 and the event was considered resolved. The investigator did not consider the event to be related to the study vaccination.

- A 17-year-old female was reported to have experienced right iliac fossa pain, dizziness, chills and articular pain. Laboratory test result *Plasmodium* test was positive. On Day 287 postvaccination 1, the participant was diagnosed with an ill-defined disorder (reported term of uncomplicated malaria, acute appendicitis, pregnancy of 22 to 24 weeks, and moderate anemia in primigravida). On Day 351 postvaccination 1, the ill-defined disorder was considered to be resolving. The investigator did not consider the event to be related to the study vaccination.
- A 28-year-old female was reported to have experienced asthenia, epigastric pain, headache, fever, and metrorrhagia with two months of amenorrhea on an unspecified day. A rapid diagnostic test for malaria and a beta-human chorionic gonadotropin hormone were positive. The participant was diagnosed with severe malaria and amenorrhea; treatment started with drotaverine and artesunate. Incomplete spontaneous abortion was reported on Day 293 postvaccination 1; an intrauterine vacuum aspiration was performed on the same day. The investigator did not consider the event to be related to the study vaccination.

Reviewer Comment: *All the non-fatal pregnancy related SAEs had a time to onset of >30 days postvaccination. None of the SAEs reported for the pregnant participants were considered related to the study vaccine by the investigator. Based on the available information no clear pattern of events exists to suggest vaccine causality.*

9.1.2 Use During Lactation

Data on use of Ervebo in lactating participants were not provided in the BLA.

9.1.3 Pediatric Use and PREA Considerations

In consultation with FDA's PeRC, CBER deferred submission of studies for all pediatric subgroups for the original BLA because the product was ready for approval for use in adults and the pediatric studies had not been completed. The following deferred pediatric studies were listed in the December 19, 2019, approval letter as the required postmarketing pediatric studies under PREA [Section 505B(a) of the Food Drug and Cosmetic Act (FDCA)]:

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

The timelines for Study V920-016 were as follows:

- Agreed iPSP: May 13, 2016
- Final protocol submission: October 21, 2016
- Study completion: January 31, 2020
- Final report submission: June 30, 2021

On April 16, 2021, FDA granted an extension of the final report submission to June 30, 2022. The Applicant submitted the results of Study V920-016 to this sBLA on June 27, 2022. On February 28, 2023, DVRPA presented the pediatric assessment to the Pediatric Review Committee (PeRC). The PeRC agreed that the product has been adequately assessed in the pediatric cohort.

Reviewer Comment: *This submission fulfills PMR # 1.*

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not applicable

10. CONCLUSIONS

Study V920-016 was submitted in accordance with Ervebo's licensing approval letter postmarketing requirement #1 in order to fulfill the PREA requirement. The study evaluated the marketed formulation of Ervebo vs placebo in a 1:1 randomized fashion. The study met its primary immunogenicity endpoint: the humoral responses in pediatric participants were non-inferior to adults. Comparison of the non-inferiority immunogenicity data in pediatric participants to adult participants allowed the FDA to bridge to the vaccine efficacy demonstrated in the ring vaccination study (V920-010) in adults. The most frequently reported adverse reactions were local and systemic solicited reactions, with pediatric subjects reporting more injection site reactions than their adult counterparts. No participants discontinued treatment or the study due to AEs. No new safety signals or patterns were identified in this study. Overall, the safety profile for Ervebo in pediatric participants and adults in this trial was generally consistent with the known safety profile of Ervebo in the approved PI.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 31. Risk-Benefit Assessment of Ervebo for the Prevention of Ebola Virus Disease in Pediatric Participants 12 Months and Older

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Zaire Ebolavirus (ZEBOV) can cause human epidemics due to human-to-human transmission via direct contact with the blood, secretions, organs or other bodily fluids of infected people or corpses and via contact with surfaces and materials contaminated with infected body fluids. • Clinical manifestations of EVD include the abrupt onset of non-specific symptoms including fever, fatigue, muscle pain, headache, and sore throat in the early stage of disease than can progress to vomiting, diarrhea, and massive fluid losses. Shock can follow, along with organ failure and hemorrhagic events, both internal and external. • Case fatality rates of 25% to 90% have been reported for EVD. • The 2014 to 2016 EVD outbreak in West Africa (Guinea, Liberia, and Sierra Leone) resulted in 28,616 cases of EVD and 11,300 deaths. • Additional ZEBOV outbreaks have occurred in West and Central Africa since the 2014 to 2016 outbreak, mainly in the DRC, resulting in over 3,700 reported cases and over 2,450 reported deaths. • Approximately 20% of all EVD cases during the epidemic in West Africa (2014) were in children <16 years, and the mortality rate in those aged <5 years was high (89.5%),	• EVD is a serious, life-threatening disease with a high risk of mortality. • High mortality rates, especially in young children, and recurring EVD outbreaks, underscore the need for an effective vaccine in children.
Unmet Medical Need	• There are currently two products licensed in the US for EVD caused by the Zaire ebolavirus: ▪ Inmazeb, a combination of three ZEBOV glycoprotein-directed human monoclonal antibodies, is indicated for the treatment of ZEBOV infection in adults and pediatric patients. ▪ Ervebo is the only vaccine licensed in the US for the prevention of ZEBOV disease in adults 18 years of age or older. • Currently, no vaccine is licensed for use in pediatric participants.	• An unmet medical need exists in the pediatric population. • Ervebo addresses an unmet medical need for EVD prevention in children.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Clinical Benefit	• One adequate and well-controlled study in participants 12 months and older was conducted and results submitted in this sBLA. • Effectiveness of Ervebo in the pediatric population was established using the non-inferiority criteria based on antibody response (GP-ELISA GMT ratio) of pediatric to adult participants at Day 28 postvaccination. • The adult clinical trial demonstrated vaccine effectiveness on a clinically meaningful endpoint to prevent disease cause by ZEBOV.	• Non-inferior GP-ELISA GMTs in the pediatric population as compared to the adult population allow for bridging the established effectiveness in adults to the pediatric population. • Immunogenicity data support extending the use of Ervebo to individuals 12 months of age and older.
Risk	• Local injection site reactions and systemic symptoms including pyrexia, headache and somnolence were commonly reported. • Injection site reactions were the most common solicited AE. • Majority of participants experienced mild local and systemic reactions within 7 days postvaccination. • The rates of SAEs through 12 months were low for the pediatric and adult participants, 2.0% vs. 1.2%, respectively and similar between treatment groups. • No SAE was considered related to Ervebo and no participant discontinued due to an AE or SAE.	• The safety profile for Ervebo in the pediatric participants in Study V920-016 is generally consistent with the known safety profile of Ervebo in the approved adult PI. • No new safety signal was identified.
Risk Management	• The most substantial risks of vaccination with Ervebo are associated with the injection site reactions. Erythema, swelling, and pain are very common. However, most injection site reactions were mild in severity, and they resolved relatively quickly without sequelae. • No other safety signals were apparent in pediatric participants 12 months and older. • The risk management plan includes routine risk minimization measures via product labeling and routine surveillance. • There are no new or reclassified safety concerns and no new updates to the PVP or Risk Mitigation Measures.	• The PVP as currently outlined is sufficient to monitor the safe use of the vaccine.

Source: FDA-generated table

11.2 Risk-Benefit Summary and Assessment

Immunogenicity and safety data submitted in this sBLA establish a substantial likelihood of benefit of Ervebo in individuals 12 months and older at risk of exposure to *Zaire ebolavirus*. Immune responses in pediatric participants were comparable to those in adult participants one-month postvaccination with the currently marketed dose and formulation of Ervebo. Risks of Ervebo include local and systemic reactogenicity of mild or moderate severity. A theoretical risk of transmitting vaccine virus from viremic vaccinees to unvaccinated contacts also exists in the first month postvaccination. In the context of the high morbidity and mortality associated with EVD in the pediatric population, the risk-benefit profile of Ervebo supports extending the indication down to individuals 12 months of age and older.

11.3 Discussion of Regulatory Options

The Applicant has requested and the data support traditional approval of Ervebo for the prevention of disease caused by *Zaire ebolavirus* in individuals 12 months of age and older.

11.4 Recommendations on Regulatory Actions

Clinical recommends approval of Ervebo for use in the pediatric population 12 months through 17 years of age. Additionally, Study V920-016 fulfills PMR #1 satisfying PREA requirements for the currently licensed dose and formulation of Ervebo for the currently licensed indication of prevention of disease caused by *Zaire ebolavirus*.

11.5 Labeling Review and Recommendations

Major changes recommended and negotiated for Ervebo included:

- Revised the indication to extend usage down to 12 months of age.
- Updated the total number of participants in the Ervebo clinical development program to reflect include pediatric and adult participants from Study V920-016.
- Added safety and immunogenicity data from Study V920-016 to support expanding usage of Ervebo to the pediatric population.
- Added data on fever events in the pediatric population.
- Added data on Ervebo shedding in pediatric participants.

11.6 Recommendations on Postmarketing Actions

CBER is not recommending or requiring any postmarketing studies.