Statistical Review and Evaluation	
Application Type	BLA (Original application)
STN	125690/0
CBER Received Date	7/15/2019
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Division / Office	Division of Vaccines and Related Product Applications (DVRPA) Office of Vaccines Research and Review (OVRR)
Committee Chair	Stephanie Polo
Clinical Reviewer	Rebecca Reindel
Project Managers	Laura Montague & Richard Daemer
Priority Review	No
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Supervisory Concurrence	Lei Huang, Concurring Reviewer, VEB/DB/OBE Tsai-Lien Lin, Branch Chief, VEB/DB/OBE John Scott, Division Director, DB/OBE
Applicant	Merck Sharp & Dohme Corp.
Established Name	Ebola Zaire Vaccine, Live
Trade Name	Ervebo
Pharmacologic Class	Vaccine
Formulation	1 mL suspension for injection supplied as a single-dose vial
Dosage Form(s) and Route(s) of Administration	A single 1 mL dose, intramuscular injection
Indication(s) and Intended Population(s)	Indicated for the prevention of disease caused by Zaire Ebolavirus in individuals 18 years of age and older

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1. Executive Summary

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

This submission includes the applicant's clinical study reports (CSRs) of two Phase 3 studies; (1) V920-010: an open label, cluster-randomized, controlled, ring vaccination study in Guinea to evaluate the efficacy and safety of the V920 Ebola vaccine, (2) V920-012: a randomized, double-blind, placebo-controlled study in US, Canada, and Spain to evaluate the safety and immunogenicity of three consecutive lots and a high-dose of V920 Ebola vaccine among healthy adults. In addition, CSRs of one Phase 2 study and one Phase 2/3 study are included in this submission; (1) V920-009: Partnership for Research on Ebola Vaccines in Liberia (PREVAIL): a Phase 2, single-center, double-blind, placebo-controlled study to evaluate the safety and the immunogenicity of V920 Ebola vaccine, (2) V920-011: Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE): a Phase 2/3, open-label, randomized study to evaluate the safety and the immunogenicity of V920 Ebola vaccine. Clinical efficacy was assessed only in study V920-010. The applicant is seeking an indication of V920 Ebola vaccine for the prevention of disease caused by Zaire Ebolavirus in individuals 18 years of age and older based on the above 4 studies and 8 Phase 1 studies performed with V920 Ebola vaccine. The focus of this review is on V920-010 and V920-012.

V920-010

The Guinea ring vaccination study (V920-010) was an open-label, cluster-randomized, controlled trial designed to evaluate the effect of one dose of V920 Ebola in preventing the disease caused by Zaire Ebolavirus among contacts and contacts of contacts of recently confirmed cases in Guinea, West Africa. During the Ebola outbreak of 2014-2016, the WHO chose this ring vaccination design based on the surveillance-containment strategy that has been implemented during the smallpox eradication campaign in the 1970s. This ring vaccination design of V920-010 was chosen to ensure that the trial was conducted in pockets of high Ebola virus disease (EVD) incidence during the declining epidemic in Guinea.

For V920-010, contacts and contacts of contacts of the confirmed index case (a person newly diagnosed with the disease caused by Zaire Ebolavirus) were identified and defined into clusters (rings) and these clusters were randomized in a 1:1 ratio to either immediate vaccination or delayed vaccination (21 days later) with a single dose of V920 (2×10^7 pfu). Subjects were followed for EVD up to 84 days following vaccination.

A total of 476 confirmed cases of EVD were identified (and reported) between 3/23/2015 and 1/20/2016 in Guinea and were evaluated for eligibility for V920-010. 361 cases were excluded (i.e. rings were not defined around them) due to (1) distance, delayed reporting, or inadequate team capacity (n=273), (2) being already included in existing rings (n=73),

(3) other reasons (n=15). Rings were defined around 115 cases and 2 additional cases from Sierra-Leone (2 rings defined in Sierra Leone were not randomized), resulting in 117 rings (11,841 contacts and contacts of contacts (CCCs) in total). Ninety-eight rings (9096 subjects) were randomized: 51 rings (4539 subjects) were randomized into the immediate vaccination arm and 47 rings (4557 subjects) were randomized to the delayed vaccination arm. Among the 19 non-randomized rings (2745 subjects), 3 were pilot rings and 16 were not randomized but instead given vaccine immediately by recommendation of the DSMB. DSMB recommendation was based on the declining number of Ebola cases in Guinea, and the observed interim vaccine efficacy (100%) although p-value at the interim (0.0036) was greater than the pre-specified α-spending criterion of 0.0027. Among 4539 subjects in the immediate vaccination arm, 2119 (47%) were eligible, consented (at Day 0) and vaccinated. Among 4557 subjects in the delayed vaccination arm, 1435 (31%) were eligible and consented at Day 0, and an additional 1104(24%) consented at Day 21.

The primary efficacy analysis was performed among subjects who were eligible and consented at Day 0 and the results are in Table 1.

Table 1: Vaccine Efficacy^ (VE) among subjects eligible and consented at Day 0 [Immediate vaccination arm vs. Delayed vaccination arm]

	# of subjects (# of rings)	# of cases at < 10 days^^ (# of affected rings)	# of cases at ≥ 10 days (# of affected rings)
Eligible, consented, and vaccinated at Day 0 in immediate vaccination arm	2119 (51)	11 (4)	0 (0)
Eligible and consented at Day 0 in delayed vaccination arm	1435 (46)	6 (5)	10 (4)

- VE = 100% with 95% CI of (63.5, 100) using the applicant's model (intra-class correlation coefficient = 0.14 was used) for estimation.
- VE = 100% with 95% CI[&] of (15.5, 100) at the ring level[#]; p-value=0.047 for testing H_0: VE = 0% using Fisher's Exact test.
- VE = 100% with 95% CI[&] of (76.5, 100) at the subject level[##]; p-value=0.00011 for testing H_0: VE = 0% using Fisher's Exact test
- Please see Table 3 in section 6.1.10 for further detail.

^ Observation period for this analysis was Day 0 to Day 31.
^^ The subjects who developed EVD before Day 10 were excluded from this analysis.
& Exact confidence interval.
# VE with 95% CI and p-value were calculated at the ring level by comparing the proportions of rings with at least one event between the two trial arms ($0/51$ vs. $4/46$); It is equivalent to using intra-class correlation coefficient = 1 in the applicant's model.
VE with 95% CI and p-value were calculated at the subject level by comparing the proportions of events between the two trial arms ($0/2108$ vs. $10/1429$); It is equivalent to using intra-class correlation coefficient = 0 in the applicant's model. This is for information purpose only.
Source: Based on the applicant's Table 11.1 in the CSR of V920-010 and my analysis.

As shown in Table 1 above, the point estimate of VE is 100% regardless of whether the estimation was based on the applicant's model with intra-class correlation = 0.14, or the estimation was at the ring level only, since there was no EVD observed in the immediate vaccination arm after Day 10. *[Estimation of VE with 95% CI at the ring level is by comparing the proportions of rings with at least one event between the two trial arms* ($0/51$ *vs.* $4/46$), *and is equivalent to assuming intra-class correlation = 1 in the*

applicant's model].The lower bound of the 95% CI of VE is 15.5% based on the estimation at the ring level, while it is 63.5% based on the applicant's model.

Since V920-010 was a field-based, open-label, and cluster-randomized study during a waning epidemic, there are potential biases and limitations in interpreting the VE estimate of 100% (Krause (*Lancet* 2015), Metzger and Vivas-Martinez (*Lancet* 2018)). However, in addition to the VE estimate being 100% with the lower bound of the 95% CI ranging from 15.5% to 76.5% depending on the model chosen, there was no EVD observed among any vaccinated subjects (n=5837 including subjects in non-randomized arm) during the period of 10 to 84 days post-vaccination. Please see further details in section 6.1.10.

Since trial-specific vaccine-safety follow-up for the subjects in the delayed vaccination arm was not initiated until after the eligible and consented subjects in this arm were vaccinated at Day 21, the safety comparison between the immediate vaccination arm vs. delayed vaccination arm from Day 0 to Day 21 (vaccinated vs. not-yet-vaccinated) could not be performed.

Among 5837 vaccinated subjects (2119 immediate, 2041 delayed, 1677 non-randomized), 65 subjects (1.1%) experienced SAEs. Febrile reaction in one subject and anaphylaxis in another subject (both resolved later) were determined by the investigator to be related to the study vaccine. Influenza-like illness in one subject (resolved later) was determined to be possibly-related to the study vaccine. Safety follow-up period for SAEs was from Day 0 to Day 84 for the subject in the immediate vaccination arm and non-randomized arm, and Day 21 to Day 105 for the subjects in the delayed vaccination arm.

V920-012

V920-012 was a randomized, placebo-controlled, double-blind, multicenter (40 in US, 1 each in Canada and Spain) trial of V920 Ebola vaccine in healthy adult subjects (18 to 65 years of age) to evaluate the safety and immunogenicity of 3 clinical consistency lots and a high dose lot of V920 compared to placebo. Subjects were randomized in a 2: 2: 2: 2: 1 ratio to received either a single vaccination from 1 of 3 consistency lots of V920 ($\geq 2x10^7$ pfu), a high dose lot of V920 ($\geq 1x10^8$ pfu), or saline placebo. The primary objectives were to evaluate the consistency in the immune responses (GP-ELISA) at 28 days post-vaccination in subjects receiving 3 consistency lots of V920, and to evaluate the safety of the Ebola vaccine. The high dose of V920 was to provide additional safety and immunogenicity data at approximately the upper threshold potency of the vaccine that would be used in the clinic.

Among 1197 enrolled subjects, 1194 (Lot A: Lot B: Lot C: High Dose: Placebo = 266: 265: 266: 264: 133) were vaccinated. The actual doses for Lots A, B, C, and High Dose were $6.6x10^7$, $6.6x10^7$, $5.4x10^7$, and $2.4x10^8$ pfu respectively. The primary analysis of lot consistency by comparing Day 28 GP-ELISA GMTs between 3 lots was performed in the Per-Protocol population. The per-protocol immunogenicity population includes all

subjects who were compliant with the protocol, received vaccination, were seronegative at Day 1 (Day 1 seronegativity defined as GP-ELISA<200), and had a serum sample at one or more timepoints. The results were as follows:

Table 2: GP-ELISA GMT ratios at Day 28 post-vaccination between 3 consistency lots A, B, and C

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

Source: Adapted from Table 11-1 in the CSR of V920-012.

As shown in Table 2 above, lot consistency was demonstrated based on the pre-specified criterion of the 95% CI of all three pair-wise GMT ratios being within (0.67, 1.50). Among 1197 enrolled subjects, 2.6% (31 subjects) had baseline GP ELISA ≥ 200 EU/mL and were excluded from Per-Protocol analysis. Day 28 (post-vaccination) GP-ELISA GMTs (with 95% CI) among subjects (Per-Protocol immunogenicity population) in Lot A, Lot B, and Lot C were 1184 EU/mL (1039, 1349), 1266 EU/mL (1108, 1446), and 1346 EU/mL (1177, 1540) respectively.

The primary analysis for safety analysis was performed on the All Subjects as Treated (ASaT) population. The ASaT population consisted of all randomized subjects who received a dose of study vaccination with safety follow-up. Eighteen (2.3%) subjects in the combined Lots A, B, and C group reported SAEs, including 2 deaths, and 3 (1.2%) subjects in the High Dose group reported SAEs, while no SAE was reported in the placebo group during Day 1 to Month 6. None of the SAEs were determined by the applicant to be related to the study vaccine.

Forty-four (5.5%) subjects (including 2 subjects who died) in the combined Lots A, B, and C group, and 9 (3.4%) subjects in the High Dose group were discontinued, while 3 (2.3%) subjects who received placebo were discontinued during Day 1 to Month 6. No subjects discontinued from the trial due to a non-fatal AE.

V920-009, V920-011

The V920-009 and V920-011 trials were originally designed to evaluate the efficacy and safety of V920 Ebola vaccine. However, efficacy was not evaluated in either of the two studies due to declining incidence of EVD in both Liberia (V920-009) and Sierra Leone (V920-011).

In the V920-009 trial, subjects (18 years and older) were randomized in a 2:1:2:1 ratio to V920 (n=500), placebo (1 mL [n=250]), ChAd3 (n=500), or placebo (2 mL [n=250]). Two different placebo groups (1mL and 2mL) were used to blind V920 and ChAd3 vaccine groups respectively. A total of 47 (9.4%) of the 500 subjects vaccinated with V920 experienced SAEs (including 5 deaths), while 59 (11.8%) of the 500 subjects who

received placebo (1 mL and 2 mL groups combined) experienced SAEs, including 6 deaths, from Day 1 to Year 1. None of the SAEs were determined by the applicant to be related to the study vaccine.

Fourteen (2.8%) subjects (including 5 subjects who died) in the V920 group and 13 (2.6%) subjects (including 6 subjects who died) in the placebo group were discontinued from Day 1 to Year 1. No subjects discontinued from the trial due to a non-fatal AE.

In the V920-011 trial, 8651 healthcare or Ebola frontline workers 18 years of age or older were randomized in a 1:1 ratio to either the immediate vaccination group (n=4319) or the deferred vaccination group (n=4332). Subjects in the immediate vaccination group were planned to be vaccinated within 7 days of enrollment, while subjects in the deferred vaccination group were planned to be vaccinated 18-24 weeks after enrollment. It was an open-label study.

A total of 55 (1.3%) subjects among 4165 vaccinees in the immediate vaccination group experienced SAEs (including 8 deaths), while 35 (0.8%) subjects among the 4332 subjects assigned to the deferred vaccination group experienced SAEs (including 6 deaths) before they received vaccination (18-24 weeks after enrollment). None of the SAEs were determined by the applicant to be related to the study vaccine.

A total of 218 (5.0%) were discontinued (including 8 deaths and 152 lost-to-follow-up) in the immediate vaccination group and 50 (1.2%) were discontinued (including 6 deaths and 32 lost-to-follow-up) in the deferred vaccination group before they received vaccination (18-24 weeks after enrollment). No subjects discontinued from the trial due to a non-fatal AE. For discussion on the imbalance between the two groups with respect to lost-to-follow-up, please see section 6.4.12.

Conclusion and Recommendation

The clinical efficacy of V920 Ebola vaccine was evaluated only in V920-010 (Guinea Ring Vaccination Study). Since there was no EVD observed in the immediate vaccination arm after Day 10, the point estimate of VE is 100% regardless of the statistical model. The lower bound of the 95% CI of VE is 15.5% based on estimation at the ring level, while it is 63.5% based on the applicant's model. The VE point estimate of 100% should be interpreted with caution because of the potential behavioral modification among the subjects in the immediate vaccination arm due to the medical study team's stay during Day 0 to Day 21 (see section 6.1.10).

There are notable constraints to interpreting the clinical evidence presented in this BLA. Specifically, the declining incidence of EVD over the period of late-phase development of the V920 Ebola vaccine along with the lack of a known correlate of protection limit the strength of evidence of effectiveness available in the application. However, within these constraints, I believe the statistical evidence presented in the BLA supports the effectiveness and safety of the V920 Ebola vaccine in the proposed indication and recommend it be approved.

2. Clinical and Regulatory Background

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

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

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

3.2 Compliance with Good Clinical Practices and Data Integrity

No data integrity issue was found.

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

5.1 Review Strategy

This submission includes the clinical study reports of V920-009, V920-010, V920-011, and V920-012. Statistical aspects of the efficacy, immunogenicity, and safety analyses were reviewed.

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

The submission of this application (STN 125690/0) was completed on 7/15/2019 and is in the EDR. The Clinical Study Reports (CSRs), electronic datasets, and Case Report Forms (CRFs) for V920-009, V920-010, V920-011, and V920-012 are in section 5.3.5.1 of this submission (STN 125690/0.0, STN 125690/0.1, and STN 125690/0.8).

6. Discussion of Individual Studies/Clinical Trials

6.1 V920-010

Title of the study: "A Randomized Trial to Evaluate Ebola Vaccine Efficacy and Safety in Guinea, West Africa"

Start date of random assignment of clusters: 4/1/2015

Discontinuation date of random assignment of clusters by DSMB recommendation: 7/31/2015. The DSMB recommendation was based on the declining number of Ebola cases in Guinea, and the observed interim vaccine efficacy (100%) although p-value at the interim (0.0036) was greater than the pre-specified α-spending criterion of 0.0027.

6.1.1 Objectives

The primary objective of this study was to evaluate the vaccine efficacy of one dose of V920 Ebola vaccine in protecting against laboratory-confirmed Ebola virus disease during 10 to 31 days post-vaccination.

The secondary objectives were to (1) evaluate safety of the vaccine by assessing SAEs over 84 days after vaccination, (2) overall vaccine effectiveness in protecting against laboratory-confirmed Ebola virus disease during 10 to 84 days post-vaccination, and (3) vaccine efficacy against EVD death (death from laboratory-confirmed Ebola virus disease).

6.1.2 Design Overview

The Guinea ring vaccination study (V920-010) was an open-label, cluster-randomized, controlled trial designed to evaluate the safety and the effect (efficacy and/or effectiveness) of one dose of V920 Ebola vaccine (rVSV-ZEBOV: a recombinant, replication competent vesicular stomatitis virus-based vaccine expressing a surface glycoprotein of Zaire Ebolavirus) in preventing the disease caused by Zaire Ebolavirus among contacts and contacts of contacts of recently confirmed cases in Guinea, West Africa. During the Ebola outbreak of 2014-2016, the WHO chose this ring vaccination design based on the surveillance-containment strategy that has been implemented during the final stages of the smallpox eradication campaign in the 1970s.

For this study, contacts and contacts of contacts of the confirmed index case (a person newly diagnosed with the disease caused by Zaire Ebolavirus) were enumerated into clusters (rings) and these clusters were randomized in a 1:1 ratio to either the immediate vaccination arm or delayed vaccination arm with a single dose of V920 Ebola virus vaccine (2×10^7 pfu). The subjects in the rings assigned to the delayed vaccination arm were vaccinated at 21 days after randomization (Day 21). Subjects were followed for Ebola virus disease (EVD) up to 84 days following vaccination.

A total of 476 confirmed cases of EVD were identified (and reported) between 3/23/2015 and 1/20/2016 in Guinea and were evaluated for eligibility for this study. Of these, 361 cases were excluded (i.e. rings were not defined around them) due to (1) distance, delayed reporting, or inadequate team capacity (n=273), (2) being already included in existing rings (n=73), (3) other reasons (n=15). Rings were defined around 115 cases and 2 additional cases from Sierra Leone, resulting in 117 rings (11,841 contacts and contacts of contacts in total). Ninety-eight rings (9096 subjects) were randomized; 51 rings (4539 subjects) into the immediate vaccination arm, and 47 rings (4557 subjects) into the

delayed vaccination arm. Among the 19 non-randomized rings (2745 subjects), 3 were pilot rings and 16 were not randomized due to DSMB recommendation.

Among 4539 subjects in the immediate vaccination arm, 2119 (47%) were eligible, consented and vaccinated at Day 0 (randomization). Among 4557 subjects in the delayed vaccination arm: (1)1435 (31%) were eligible and consented at Day 0, (2) 1104 (24%) were eligible and consented at Day 21. Among 1435 subjects eligible and consented at Day 0 in the delayed vaccination arm, 940 were vaccinated at Day 21. Among 1104 subjects eligible and consented at Day 21 in the delayed vaccination arm, 1101 were vaccinated at Day 21.

6.1.3 Population

The primary efficacy analysis was performed on the population of the subjects eligible, consented and vaccinated at Day 0 in the immediate vaccination arm (n=2119) vs. the population of subjects eligible and consented at Day 0 in the delayed vaccination arm (n=1435).

The safety was evaluated on the subjects eligible, consented (at Day 0 or at Day 21), and vaccinated (n=5837: 2119 in the immediate vaccination arm, 2041 in the delayed vaccination arm, and 1677 in the non-randomized arm). No comparative safety analysis could be performed by comparing subjects in the immediate vaccination arm vs. subjects in the delayed vaccination arm during Day 0 to Day 21, since trial-specific vaccine-safety follow-up for subjects in the delayed vaccination arm was not started until after the subjects in this arm were vaccinated at Day 21.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Immediate Vaccination Arm: V920 rVSV-ZEBOV (a recombinant, replication competent vesicular stomatitis virus-based vaccine expressing a surface glycoprotein of Zaire Ebolavirus) at Day 0. (The vaccine dose of $\geq 2x10^7$ pfu was injected intramuscularly (IM) as a single dose of 1 mL in the deltoid muscle.)

Delayed Vaccination Arm: V920 rVSV-ZEBOV at Day 21. It is an open-label study. No placebo was administered at Day 0 for this arm.

Non-Randomized Arm: V920 rVSV-ZEBOV at Day 0.

6.1.6 Sites and centers

N/A.

This was a field-based, ring-vaccination study. Rings were defined around 115 Ebola cases in Guinea and 2 additional Ebola cases from Sierra Leone, resulting in 117 rings (11,841 contacts and contacts of contacts (CCCs) in total). Ninety-eight rings (9096 subjects) were randomized: 51 rings (4539 subjects) were randomized into the immediate

vaccination arm and 47 rings (4557 subjects) were randomized into the delayed vaccination arm. Among 19 non-randomized rings (2745 subjects), 3 were pilot rings and 16 were not randomized due to DSMB recommendation. Two rings from Sierra-Leone were not randomized.

6.1.7 Surveillance/Monitoring

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

6.1.8 Endpoints and Criteria for Study Success

Efficacy endpoint: The primary efficacy endpoint was laboratory-confirmed Ebola virus disease (EVD), during 10 to 31 days post-vaccination, defined as: (1) any probable[1] or suspected[2] case from whom a blood sample taken was laboratory-confirmed as positive for EVD; or (2) any deceased individual with probable EVD, from whom a post-mortem sample taken within 48 hours after death was laboratory-confirmed as positive for EVD. Laboratory confirmation was obtained though the local laboratories of the national Ebola surveillance system by detection of virus RNA using real time reverse transcriptase-polymerase chain reaction (RT-PCR). This testing was performed independently of the trial team by various international Ebola surveillance laboratories.

Safety endpoints: The primary safety endpoint was serious adverse events (SAEs) over 84 days post vaccination. Reactogenicity within 30 minutes post vaccination and solicited and unsolicited AEs on Days 3, 14, 21, 42, 63 and 84 were also evaluated. Trial-specific vaccine-safety follow-up for the subjects in the delayed vaccination arm was not initiated until after the eligible and consented subjects in this arm were vaccinated at Day 21.

6.1.9 Statistical Considerations and Statistical Analysis Plan

The primary efficacy hypothesis tested was

H_0: VE = 0 vs. H_a: VE $\neq$ 0

where VE [Vaccine Efficacy against EVD] = 1 - $\lambda_{IV}/\lambda_{DV}$,

λ_{IV} = hazard of EVD for individuals in the immediate vaccination arm,

λ_{DV} = hazard of EVD for individuals in the delayed vaccination arm.

[1] Probable EVD: Any suspected case evaluated by a clinician OR any person who died from suspected EVD and had an epidemiological link to a confirmed case but was not tested and did not have laboratory confirmation of the disease.

[2] Suspected EVD: Any person, alive or dead, who has (or had) sudden onset of high fever and had contact with a suspected, probable or confirmed EVD case, or a dead or sick animal OR any person with sudden onset of high fever and at least three of the following symptoms: headache, vomiting, anorexia/loss of appetite, diarrhea, lethargy, stomach pain, aching muscles or joints, difficulty swallowing, breathing difficulties, or hiccup; OR any person with unexplained bleeding OR any sudden, unexplained death.

The applicant originally proposed to use a mixed-effects, time-dependent, Cox regression model with a random effect (frailty). However, the Cox regression model could not be used, since no EVD case was observed in immediate vaccination arm.

For the estimation of VE with a 95% confidence interval (CI), the applicant fitted a beta-binomial distribution to the ring-level numerators and denominators and used an inverted likelihood ratio test to estimate the lower bound of 95% CI for hazard ratio ($\lambda_{IV}/\lambda_{DV}$). However, for calculating p-value in testing H_0: VE = 0, Fisher's exact test was used to compare the proportions of rings with at least one event between the two trial arms.

6.1.10 Primary Efficacy Analyses

The primary efficacy analysis was performed by comparing the population of subjects eligible, consented and vaccinated at Day 0 in the immediate vaccination arm (n=2119) vs. the population of subjects eligible and consented at Day 0 in the delayed vaccination arm (n=1435) with respect to the laboratory-confirmed Ebola virus disease (EVD) observed during Day 10 to Day 31 (post-randomization). The subjects who developed EVD before Day 10 were excluded from this analysis in consideration of (i) incubation period of EVD, (ii) the time between onset of symptoms and laboratory confirmation, and (iii) the unknown period between vaccination and a vaccine-induced protective immune response (lag-period). This analysis could be regarded as per-protocol analysis. Table 3 shows the results of primary efficacy analysis:

Table 3: Vaccine Efficacy^ (VE) among subjects eligible and consented at Day 0 [Immediate vaccination arm vs. Delayed vaccination arm]

	# of subjects (# of rings)	# of cases at < 10 days^^ (# of affected rings)	# of cases at ≥ 10 days (# of affected rings)
Eligible, consented, and vaccinated at Day 0 in immediate vaccination arm	2119 (51)	11 (4)	0 (0)
Eligible and consented at Day 0 in delayed vaccination arm	1435 (46)	6 (5)	10 (4)

(a) Vaccine Efficacy (VE) = 100% with 95% CI of (63.5, 100) using the applicant's model (intra-class correlation coefficient =0.14 was used) for estimation
(b) Vaccine Efficacy (VE) = 100% with 95% CI& of (15.5, 100) *at the ring level*; p-value=0.047 for testing H_0: VE = 0% using Fisher's Exact test
(c) Vaccine Efficacy (VE) = 100% with 95% CI& of (76.5, 100) *at the subject level*; p-value=0.00011 for testing H_0: VE = 0% using Fisher's Exact test

^ Observation period for this analysis was Day 0 to Day 31.
^^ The subjects who developed EVD before Day 10 were excluded from this analysis.
& Exact confidence interval.
(b) VE and p-value were calculated *at the ring level* by comparing the proportions of rings with at least one event between the two trial arms (0/51 vs. 4/46); It is equivalent to assuming intra-class correlation coefficient =1 in the applicant's model in (a).
(c) VE and p-value were calculated *at the subject level* by comparing the proportions of events between the two trial arms (0/2108 vs. 10/1429); It is equivalent to assuming intra-class correlation coefficient=0 in the applicant's model in (a). This is for information purpose only.
Source: Based on the applicant's Table 11.1 in the CSR of V920-010 and my analysis.

As shown in Table 3 above, the point estimate of VE is 100% regardless of whether the estimation was based on the applicant's model with intra-class correlation coefficient =

0.14, or the estimation was at the ring level, or the estimation was at the subject level, since there was no EVD observed in the immediate vaccination arm after Day 10.The lower bound of the 95% CI of VE varies from 15.5% to 76.5% depending on the model chosen based on different assumed intra-class correlation coefficient. The most conservative analysis is the one at the ring level; this analysis assumes that no case after the first one in any ring contributes any additional information.

Since V920-010 was a field-based, open-label, and cluster-randomized study during a waning epidemic, there are potential biases and limitations in estimating and interpreting VE (Krause (*Lancet* 2015), Metzger and Vivas-Martinez (*Lancet* 2018)):

(1) 'The medical study team(s) (for safety follow-up) visited rings randomized to delayed vaccination arm at Day 0 and did not return until Day 21, while the medical study team(s) stayed from Day 0 in the rings randomized to immediate vaccination arm. Thus, the perfect VE could be regarded as over-estimation of the true VE due to the behavioral change (among the subjects in rings randomized to immediate vaccination arm) influenced by the medical study team's stay from Day 0.' This concern was raised by Metzger and Vivas-Martinez (*Lancet* 2018). The investigators' (Longini et.al. (*Lancet* 2018)) response was that (among the 3232 eligible subjects in the immediate vaccination arm, 1081 subjects did not consent and did not get vaccinated) 'Among those 1081, there were 8 EVDs observed at Day 10 more after randomization. Thus, if vaccination had no effect and the presence of medical staff explained the entire effect, this number should be zero or very small.' My opinion is that the investigators' response could be valid only if the un-consented subjects in the immediate vaccination arm were influenced by the medical study team's stay *as much as* the consented subjects were. However, there is no way to measure the difference in the extent of medical team's influence between the consenters and the non-consenters in the immediate vaccination arm.

(2) 'Since clusters (not individuals) were randomly assigned and infection risks of individuals within clusters are not independent (e.g., one cluster contributed six cases of Ebola virus disease, which is more than the others), the most relevant analyses are done at the cluster level.' This comment was made by Krause (*Lancet* 2015). I performed the analysis at the ring (cluster) level as shown in Table 3; VE = 100% with 95% CI of (15.5, 100). The lower bound of the 95% CI of VE is 15.5% based on the ring level analysis, while it is 63.5% based on the applicant's model (intra-class coefficient = 0.14 was used).

(3) [Krause's (*Lancet* 2015) comment continued from (2)] 'However, differences in the composition of the analysis groups for immediate versus delayed vaccination rings led to an imbalance: immediate vaccination rings included an average of 42 participants (2014 people in 48 clusters) and delayed vaccination rings included an average of 57 participants (2380 people in 42 clusters) whose outcome contributed to the primary analysis. The larger number of people per cluster in the delayed vaccination rings increased the chance that Ebola would be diagnosed in

these rings, biasing the cluster-level primary statistical analysis in favour of the vaccine.' [Please note that numbers in this comment are from the interim analysis, since the comment was made for the interim analysis]. This is true. However, the primary efficacy analysis was performed by comparing the population of subjects eligible, consented and vaccinated at Day 0 in the immediate vaccination arm (2119 subjects in 51 rings; average ring size=41.5) vs. the population of subjects eligible and consented at Day 0 in the delayed vaccination arm (1435 in 46 rings; average ring size=31.2) with respect to the laboratory-confirmed Ebola virus disease (EVD) observed during Day 10 to Day 31 (post-randomization). Thus, the ring (cluster) level primary efficacy analysis is not weighted in favor of the vaccine in the sense of this comment.

(4) Krause (*Lancet* 2015) suggested some additional analyses:

(a) 'the intention-to-treat analysis, comparing the incidence of Ebola virus disease in all individuals eligible for either immediate (six cases of disease) versus delayed (16 cases) vaccination' [Please note that numbers in this comment are from the interim analysis, since the comment was made for the interim analysis]. This intent-to-treat analysis was performed, and result is in Table 4 below:

Table 4: VE^ among eligible subjects
[Immediate vaccination arm vs. Delayed vaccination arm]

	# of subjects (# of rings)	# of cases at < 10 days^^ (# of affected rings)	# of cases at ≥ 10 days (# of affected rings)
Eligible in immediate vaccination arm	3232 (51)	20 (9)	7$ (4)
Eligible in delayed vaccination arm	3096 (47)	21 (14)	16 (7)

(a) Vaccine Efficacy (VE) = 64.6% with 95% CI of (-43.6, 91.3) using Cox proportional hazard model for estimation
(b) Vaccine Efficacy (VE) = 47.3% with 95% CI& of (-68.5, 89.5) *at the ring level*; p-value=0.34 for testing H_0: VE = 0% using Fisher's Exact test
(c) Vaccine Efficacy (VE) = 58.1% with 95% CI& of (0.44, 86.8) *at the subject level*; p-value=0.059 for testing H_0: VE = 0% using Fisher's Exact test

^ Observation period for this analysis was Day 0 to Day 31.
^^ The subjects who developed EVD before Day 10 were excluded from this analysis.
& Exact confidence interval.
$ All 7 cases occurred in the un-vaccinated subjects (n=1113). There were no EVD case among vaccinated (n=2119) on or after Day 10. Please see Table 5.
(b) VE and p-value were calculated *at the ring level* by comparing the proportions of rings with at least one event between the two trial arms (4/51 vs. 7/47).
(c) VE and p-value were calculated *at the subject level* by comparing the proportions of events between the two trial arms (7/3212 vs. 16/3075).
Source: Based on the applicant's Table 11.1 in the CSR of V920-010 and my analysis.

As seen in Table 4, the lower bound of the 95% CI for VE is negative or close to 0 in all models. However, it should be noted that all 7 EVD cases observed among eligible subjects in the immediate vaccination arm on or after Day 10 were un-vaccinated subjects.

(b) 'a comparison of Ebola virus disease incidence within the immediate vaccination rings of those actually vaccinated versus those who were not vaccinated' As shown in Table 5 below, there were no EVD case among vaccinated (n=2119) on or after Day 10.

Table 5: Comparison of EVD incidence within the immediate vaccination rings of those actually vaccinated vs. those who were not vaccinated

	# of subjects (# of rings)	# of cases at < 10 days (# of affected rings)	# of cases at ≥ 10 days (# of affected rings)
Eligible and *vaccinated* in immediate vaccination arm	2119 (51)	11 (4)	0 (0)
Eligible and *not-vaccinated* in immediate vaccination arm	1113 (48)	9 (7)	7 (4)
Eligible in immediate vaccination arm	3232 (51)	20 (9)	7 (4)

^ Observation period for this analysis was Day 0 to Day 31.
Source: Adapted from Table 11.1 in the CSR of V920-010.

(c) 'a comparison of Ebola incidence after vaccination, of individuals in both the immediate and delayed vaccination clusters, before the 10-day post-vaccination cutoff versus after the cutoff' There were 11 EVD cases observed before the 10-day post-vaccination cutoff among 2119 vaccinated subjects in the immediate vaccination arm. There were 4 EVD cases observed before the 10-day post-vaccination cutoff among 2041 vaccinated subjects in the delayed vaccination arm. However, there was no EVD observed among any vaccinated subjects during the period 10 to 84 days post-vaccination.

Additional efficacy analyses were performed (as sensitivity analyses):

(A) by comparing the population of subjects eligible, consented and vaccinated at Day 0 in the immediate vaccination arm (n=2119) vs. the population of subjects eligible and consented at Day 0 or Day 21 in the delayed vaccination arm (n=2539) with respect to the laboratory-confirmed Ebola virus disease (EVD) observed during Day 10 to Day 31 (post randomization). Table 6 shows the results of this analysis.

Table 6: VE^ by comparing the population of subjects eligible, consented and vaccinated at Day 0 in the immediate vaccination arm vs. the population of subjects eligible and consented at Day 0 or Day 21 in the delayed vaccination arm

	# of subjects (# of rings)	# of cases at < 10 days^^ (# of affected rings)	# of cases at ≥ 10 days (# of affected rings)
Eligible, consented, and vaccinated at Day 0 in immediate vaccination arm	2119 (51)	11 (4)	0 (0)
Eligible and consented at Day 0 or Day 21 in delayed vaccination arm	2539 (47)	6 (5)	11 (5)

(a) Vaccine Efficacy (VE) = 100% with 95% CI of (60.1, 100) using the applicant's model (intra-class correlation coefficient=0.14 was used) for estimation

(b) Vaccine Efficacy (VE) = 100% with 95% CI& of (32.1, 100) *at the ring level*; p-value=0.023 for testing H_0: VE = 0% using Fisher's Exact test

(c) Vaccine Efficacy (VE) = 100% with 95% CI& of (61.9, 100) *at the subject level*; p-value=0.0014 for testing H_0: VE = 0% using Fisher's Exact test

^ Observation period for this analysis was Day 0 to Day 31.

^^ The subjects who developed EVD before Day 10 were excluded from this analysis.

& Exact confidence interval.

(b) VE and p-value were calculated *at the ring level* by comparing the proportions of rings with at least one event between the two trial arms ($0/51$ vs. $5/47$); It is equivalent to assuming intra-class correlation coefficient=1 in the applicant's model in (a).

(c) VE and p-value were calculated *at the subject level* by comparing the proportions of events between the two trial arms ($0/2108$ vs. $11/2533$); It is equivalent to assuming intra-class correlation coefficient=0 in the applicant's model in (a).

Source: Based on the applicant's Table 11.1 in the CSR of V920-010 and my analysis.

(B) by comparing the population of subjects eligible, consented and vaccinated at Day 0 in the immediate vaccination arm (n=2119) vs. the population of subjects eligible in the delayed vaccination arm (n=3096) with respect to the laboratory-confirmed Ebola virus disease (EVD) observed during Day 10 to Day 31 (post randomization). Table 7 shows the results of this analysis.

Table 7: VE^ by comparing the population of subjects eligible, consented and vaccinated at Day 0 in the immediate vaccination arm vs. the population of subjects eligible in the delayed vaccination arm

	# of subjects (# of rings)	# of cases at < 10 days^^ (# of affected rings)	# of cases at ≥ 10 days (# of affected rings)
Eligible, consented, and vaccinated at Day 0 in immediate vaccination arm	2119 (51)	11 (4)	0 (0)
Eligible in delayed vaccination arm	3096 (47)	21 (14)	16 (7)

(a) Vaccine Efficacy (VE) = 100% with 95% CI of (68.9, 100) using the applicant's model (intra-class correlation coefficient=0.14 was used) for estimation

(b) Vaccine Efficacy (VE) = 100% with 95% CI& of (53.8, 100) *at the ring level*; p-value=0.0045 for testing H_0: VE = 0% using Fisher's Exact test

(c) Vaccine Efficacy (VE) = 100% with 95% CI& of (69.1, 100) *at the subject level*; p-value=0.00039 for testing H_0: VE = 0% using Fisher's Exact test

^ Observation period for this analysis was Day 0 to Day 31.

^^ The subjects who developed EVD before Day 10 were excluded from this analysis.

& Exact confidence interval.

(b) VE and p-value were calculated *at the ring level* by comparing the proportions of rings with at least one event between the two trial arms ($0/51$ vs. $7/47$); It is equivalent to assuming intra-class correlation coefficient=1 in the applicant's model in (a).

(c) VE and p-value were calculated *at the subject level* by comparing the proportions of events between the two trial arms ($0/2108$ vs. $16/3075$); It is equivalent to assuming intra-class correlation coefficient=0 in the applicant's model in (a).

Source: Based on the applicant's Table 11.1 in the CSR of V920-010 and my analysis.

(C) by comparing the population of subjects eligible and consented at Day 0 in the immediate vaccination arm (n=2151) vs. the population of subjects eligible and consented at Day 0 or Day 21 in the delayed vaccination arm (n=2539) with respect to the laboratory-confirmed Ebola virus disease (EVD) observed during Day 10 to Day 31 (post randomization). Table 8 shows the results of this analysis.

Table 8: VE^ by comparing the population of subjects eligible and consented at Day 0 in the immediate vaccination arm vs. the population of subjects eligible and consented at Day 0 or Day 21 in the delayed vaccination arm

	# of subjects (# of rings)	# of cases at < 10 days^^ (# of affected rings)	# of cases at ≥ 10 days (# of affected rings)
Eligible, consented at Day 0 in immediate vaccination arm	2151 (51)	11 (4)	0 (0)
Eligible and consented at Day 0 or 21 in delayed vaccination arm	2539 (47)	6 (5)	11 (5)

(a) Vaccine Efficacy (VE) = 100% with 95% CI of (60.6, 100) using the applicant's model (intra-class correlation coefficient=0.14 was used) for estimation

(b) Vaccine Efficacy (VE) = 100% with 95% CI& of (32.1, 100) *at the ring level*; p-value=0.023 for testing H_0: VE = 0% using Fisher's Exact test

(c) Vaccine Efficacy (VE) = 100% with 95% CI& of (62.4, 100) *at the subject level*; p-value=0.0013 for testing H_0: VE = 0% using Fisher's Exact test

^ Observation period for this analysis was Day 0 to Day 31.

^^ The subjects who developed EVD before Day 10 were excluded from this analysis.

& Exact confidence interval.

(b) VE and p-value were calculated *at the ring level* by comparing the proportions of rings with at least one event between the two trial arms ($0/51$ vs. $5/47$); It is equivalent to assuming intra-class correlation coefficient=1 in the applicant's model in (a).

(c) VE and p-value were calculated *at the subject level* by comparing the proportions of events between the two trial arms ($0/2140$ vs. $11/2533$); It is equivalent to assuming intra-class correlation coefficient=0 in the applicant's model in (a).

Source: Based on the applicant's Table 11.1 in the CSR of V920-010 and my analysis.

6.1.11 Secondary Efficacy Analyses

The primary efficacy analysis was performed by comparing the population of subjects eligible, consented and vaccinated at Day 0 in the immediate vaccination arm (n=2119) vs. the population of subjects eligible and consented at Day 0 in the delayed vaccination arm (n=1435) with respect to the laboratory-confirmed Ebola virus disease (EVD) observed during Day 10 to Day 31. As secondary efficacy analyses, the following were performed:

- Overall vaccine effectiveness in protecting against laboratory-confirmed Ebola virus disease during 10 to 84 days post-vaccination. Absolute vaccine efficacy based on comparing vaccinated vs. unvaccinated during 10 to 84 days post-vaccination could not be estimated, because subjects assigned to delayed vaccination group were vaccinated at Day 21. However, among all vaccinated (n=5837; all three arms immediate, delayed, and non-randomized combined), there was no EVD observed during 10 to 84 days post-vaccination.

- VE against EVD death are shown in Table 9:

Table 9: VE^ against EVD death among subjects eligible and consented at Day 0 [Immediate vaccination arm vs. Delayed vaccination arm]

	# of subjects (# of rings)	# of cases at < 10 days^^ (# of affected rings)	# of **EVD deaths** with onset of symptoms ≥ 10 days (# of affected rings)
Eligible, consented, and vaccinated at Day 0 in immediate vaccination arm	2119 (51)	11 (4)	0 (0)
Eligible and consented at Day 0 in delayed vaccination arm	1435 (46)	6 (5)	8 (4)
(a) Vaccine Efficacy (VE) = 100% with 95% CI of (64.3, 100) using the applicant's model for estimation (b) Vaccine Efficacy (VE) = 100% with 95% CI& of (15.5, 100) *at the ring level*; p-value=0.047 for testing H_0: VE = 0% using Fisher's Exact test (c) Vaccine Efficacy (VE) = 100% with 95% CI& of (69.5, 100) *at the subject level*; p-value=0.0007 for testing H_0: VE = 0% using Fisher's Exact test			

^ Observation period for this analysis was Day 0 to Day 31.
^^ The subjects who developed EVD before Day 10 were excluded from this analysis.
& Exact confidence interval.
(b) VE and p-value were calculated *at the ring level* by comparing the proportions of rings with at least one event between the two trial arms (0/51 vs. 4/46).
(c) VE and p-value were calculated *at the subject level* by comparing the proportions of events between the two trial arms (0/2108 vs. 8/1429).
Source: Based on the applicant's Table 11.1 in the CSR of V920-010 and my analysis.

6.1.12 Safety Analyses

Since trial-specific vaccine safety follow-up for the subjects in the delayed vaccination arm was not initiated until after the eligible and consented subjects in this arm were vaccinated at Day 21, the safety comparison between immediate vaccination arm vs. delayed vaccination arm from Day 0 to Day 21 (vaccinated vs. not-yet-vaccinated) could not be performed.

Among the 5837 (Immediate: Delayed: Non-Randomized = 2119: 2041: 1677) vaccinated subjects, 65 (1.1%) subjects experienced SAEs. Febrile reaction in one subject and anaphylaxis in another subject (both resolved later) were determined by the investigator to be related to the study vaccine. Influenza-like illness in one subject (resolved later) was determined to be possibly-related to the study vaccine. A total of 18 (0.3%) deaths were reported. Of those 18 deaths, 12 were EVD-related. The time intervals from vaccination to the onset of EVD were 8 days or less for those 12 EVD-related deaths.

Safety follow-up period for SAEs was from Day 0 to Day 84 for the subject in the immediate vaccination arm and non-randomized arm, and Day 21 to Day 105 for the subjects in the delayed vaccination arm.

During the period from Day 0 to Day 10, there were 11 (0.52%) EVDs observed among 2119 eligible, consented (at Day 0), and vaccinated subjects in the immediate vaccination arm, while there were 6 (0.42%) EVDs observed among 1435 eligible and consented (at Day 0) subjects in the delayed vaccination arm.

6.1.13 Subgroup Analyses of the Primary Efficacy Endpoint

The primary efficacy analysis was performed by comparing the population of subjects eligible, consented and vaccinated at Day 0 in the immediate vaccination arm (n=2119) vs. the population of subjects eligible and consented at Day 0 in the delayed vaccination arm (n=1435) with respect to the laboratory-confirmed Ebola virus disease (EVD) observed during Day 10 to Day 31. There was no EVD observed among 2119 subjects in the immediate vaccination arm during Day 10 to Day 31. There were 10 EVDs observed among 1435 subjects in the delayed vaccination arm during Day 10 to day 31. The disease attack rate is too low (and the number of cases is too small) to perform any meaningful subgroup analyses. However, the distribution of sex (male, female) and age among 10 EVD cases observed is similar to the distribution of sex and age among 1435 subjects in the delayed vaccination arm at baseline.

6.2 V920-012

Title of the study: "A Phase 3, Randomized, Placebo-Controlled, Clinical Trial to Study the Safety and Immunogenicity of Three Consistency Lots and a High Dose Lot of rVSV-ZEBOV-GP (V920 Ebola Vaccine) in Healthy Adults"

Study start date: 8/17/2015
Study completion date: 5/2/2016

6.2.1 Objectives

The primary objectives of this study were:

(1) to demonstrate that vaccination with V920 Ebola vaccine from 3 separate consistency lots (A, B, and C) results in equivalent immunogenicity (antibody titers as measured by GP-ELISA at Day 28 post-vaccination).
(2) to evaluate the safety of V920 from 3 consistency lots (A, B, and C each separately and combined) and the High Dose group through 42 days post-vaccination.

The secondary objectives were:

(1) to estimate the geometric mean titers (GMTs) of antibodies as measured by GP-ELISA at Day 28 post-vaccination in the 3 consistency lots (A, B, and C combined) and the High Dose group.
(2) to estimate the GMTs of neutralizing antibodies measured by plaque reduction neutralization test (PRNT) at 28 days post-vaccination in the 3 consistency lots (A, B, and C combined) and the High Dose group.

6.2.2 Design Overview

V920-012 was a randomized, placebo-controlled, double-blind, multicenter (40 in US, 1

each in Canada and Spain) trial of V920 Ebola vaccine in healthy adult subjects (18 to 65 years of age) to evaluate the safety and immunogenicity of 3 clinical consistency lots and a high dose lot of V920 compared to placebo. Subjects were randomized in a 2: 2: 2: 2: 1 ratio to received either a single vaccination from 1 of 3 consistency lots of V920 ($\geq 2x10^7$ pfu), a high dose lot of V920 ($\geq 1x10^8$ pfu), or placebo (saline). The primary objectives were to evaluate the consistency in the immune responses (GP-ELISA) through 28 days postvaccination of subjects receiving 3 consistency lots of V920, and to evaluate the safety of the consistency lots. The high dose of V920 was to provide additional safety and immunogenicity data at approximately the upper threshold potency of the vaccine that would be used in the clinic.

Among 1197 enrolled subjects, 1194 (Lot A: Lot B: Lot C: High Dose: Placebo = 266: 265: 266: 264: 133) were vaccinated. The actual doses for Lots A, B, C, and High Dose were $6.6x10^7$, $6.6x10^7$, $5.4x10^7$, and $2.4x10^8$ pfu respectively.

6.2.3 Population

The primary analysis of lot consistency by comparing Day 28 GP-ELISA GMTs between 3 lots were performed in the Per-Protocol immunogenicity population. The per-protocol immunogenicity population includes all subjects who were compliant with the protocol, received vaccination, were seronegative at Day 1 (Day 1 seronegativity defined as GP-ELISA<200), and had a serum sample at one or more timepoints.

The primary population for safety analysis was the All Subjects as Treated (ASaT) population. The ASaT population consisted of all randomized subjects who received a dose of study vaccination with safety follow-up. [Subjects were included in the treatment group corresponding to the study vaccine they actually received for the analysis of safety.]

6.2.4 Study Treatments or Agents Mandated by the Protocol

Lot A: V920 rVSV-ZEBOV (a recombinant, replication competent vesicular stomatitis virus-based vaccine expressing a surface glycoprotein of Zaire Ebolavirus) [The vaccine dose of $\geq 2x10^7$ pfu (nominal dose); $6.6x10^7$ pfu (actual dose) injected intramuscularly (IM) as a single dose of 1 mL in the deltoid muscle.]

Lot B: V920 rVBSV-ZEBOV [The vaccine dose of $\geq 2x10^7$ pfu (nominal dose); $6.6x10^7$ pfu (actual dose) injected intramuscularly (IM) as a single dose of 1 mL in the deltoid muscle.]

Lot C: V 920 rVSV-ZEBOV [The vaccine dose of $\geq 2x10^7$ pfu (nominal dose); $5.4x10^7$ pfu (actual dose) injected intramuscularly (IM) as a single dose of 1 mL in the deltoid muscle.]

High Dose group: V 920 rVSV-ZEBOV [The vaccine dose of $\geq 1x10^8$ pfu (nominal dose); $2.4x10^8$ pfu (actual dose) injected intramuscularly (IM) as a single dose of 1 mL in the deltoid muscle.]

Placebo group: Normal saline 0.9% injected intramuscularly (IM) as a single dose of 1 mL in the deltoid muscle.

6.2.6 Sites and centers

This study was conducted at 42 centers: 40 in the United States, 1 in Canada, and 1 in Spain.

6.2.7 Surveillance/Monitoring

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

6.2.8 Endpoints and Criteria for Study Success

Immunogenicity endpoints: The primary immunogenicity endpoint was the antibody titers as measured by GP-ELISA at Day 28 post-vaccination. The criterion for the study success in terms of immunogenicity (lot consistency) was the two-sided 95% confidence interval (CI) on each of the pairwise lot-to-lot comparisons of the GP-ELISA (EU/ml) GMT ratios being greater than 0.67-fold and less than 1.5-fold. The secondary immunogenicity endpoint was the neutralizing antibody titers as measured by plaque reduction neutralization test (PRNT) at 28 days post-vaccination.

Safety endpoints: The primary safety endpoint was SAEs (Day 1 to Month 6 post-vaccination). The secondary safety endpoints were:

(a) Vaccination report card (VRC) -prompted injection site adverse events: redness, swelling, and pain/tenderness/soreness (Day 1 to Day 5 postvaccination) after any study vaccination.
(b) VRC-prompted elevated temperature ($\geq 38.0^{\circ}C$ [$\geq 100.4^{\circ}$ F] oral or equivalent) (Days 1 to 42 postvaccination).
(c) Days 5 to 42 post-vaccination arthralgia and arthritis.
(d) Days 1 to 42 post-vaccination: rash; vesicular lesions; petechial/purpuric rash; vesicular lesions with rash; vesicular lesions with rash and fluid was collected with the vesicles; vesicular lesions without rash; vesicular lesions without rash and fluid was collected from vesicles.

6.2.9 Statistical Considerations and Statistical Analysis Plan

The primary immunogenicity hypotheses tested were, for each of the three pair-wise comparisons between lots A, B, and C,

H_{01}: $GMT_A/GMT_B \geq 1.5$ or $GMT_A/GMT_B \leq 0.67$
H_{02}: $GMT_A/GMT_C \geq 1.5$ or $GMT_A/GMT_C \leq 0.67$

H_{03}: $GMT_B/GMT_C \geq 1.5$ or $GMT_B/GMT_C \leq 0.67$

where GMT_I (I=A, B, or C) is the geometric mean titer of anti-ZEBOV GP antibody measured by GP-ELISA at 28 days post-vaccination.

To demonstrate lot consistency between the three lots, all three hypotheses need to be rejected.

The primary hypotheses were tested based on an Analysis of Variance (ANOVA) to demonstrate lot consistency. The ANOVA modeled the log of the GP-ELISA (EU/ml) levels of the subjects at Day 28 post-vaccination as a function of consistency lot (A, B, and C) and categorical age (18-45 and 46-65).

6.2.10 Primary Immunogenicity Analyses

The primary analysis of lot consistency by comparing Day 28 GP-ELISA GMTs between 3 lots were performed in the Per-Protocol immunogenicity population. The per-protocol immunogenicity population includes all subjects who were compliant with the protocol, received vaccination, were seronegative at Day 1 (Day 1 seronegativity defined as GP-ELISA<200), and had a serum sample at one or more timepoints. Among 1197 enrolled subjects, 2.6% (31 subjects) had baseline GP ELISA ≥ 200 EU/mL and were excluded from Per-Protocol analysis.

As shown in Table 10, for each of the pair-wise comparisons between the lots, the lower bound of the 95% CI of the GMT ratio between the groups being compared was greater than 0.67 and the upper bound was less than 1.5, demonstrating lot consistency based on the pre-specified criterion.

Table 10: GP-ELISA GMT ratios at Day 28 post-vaccination between 3 consistency lots A, B, and C

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

Source: Adapted from Table 11-1 in the CSR of V920-012.

6.2.11 Secondary Immunogenicity Analyses

The secondary immunogenicity analyses were performed on the Per-Protocol immunogenicity population.

GMTs (with 95% CI) of antibodies as measured by GP-ELISA at Day 28 and Month 6 post-vaccination were estimated and the results are in Table 11:

Table 11^: GMTs with 95% CI for GP-ELISA
[Per-Protocol^^ Immunogenicity Population]

	Baseline	Day 28	Month 6
Lot A	<LLOQ	1184 (1039, 1349)	1052 (920, 1203)
Lot B	<LLOQ	1266 (1108, 1446)	1060 (926, 1214)
Lot C	<LLOQ	1346 (1177, 1540)	1241 (1082, 1424)
Combined Lot	<LLOQ	1262 (1169, 1363)	1113 (1030, 1204)
High Dose	<LLOQ	1292 (1127, 1481)	1190 (1037, 1365)
Placebo	<LLOQ	<LLOQ	<LLOQ

^ LLOQ for GP-ELISA was 36.11 EU/mL; if <LLOQ, then LLOQ/2 was assigned.
^^ 31 subjects (2.6%) had baseline GP ELISA ⩾ 200 EU/mL and were excluded from Per-Protocol analysis.
Source: Adapted from Table 11-2 in the CSR of V920-012.

Percentage of subjects with 2-fold increase from baseline titer and ≥200 EU/mL was shown in Table 12 with 95% CI at Day 28 and Months 6.

Table 12^: Percentage (with 95% CI) of subjects with 2-fold increase from baseline titer and ≥200 EU/mL
[Per-Protocol^^ Immunogenicity Population]

	Day 28	Month 6
Lot A	94.1% (90.4, 96.8)	95.1% (91.5, 97.5)
Lot B	97.8% (95.0, 99.3)	95.0% (91.3, 97.5)
Lot C	94.2% (90.4, 96.9)	95.4% (91.7, 97.8)
Combined Lot	95.4% (93.6, 96.8)	95.2% (93.3, 96.7)
High Dose	98.2% (95.4, 99.5)	96.3% (92.8, 98.4)
Placebo	0.8% (0.0, 4.4)	0.8% (0.0, 4.5)

^ LLOQ for GP-ELISA was 36.11 EU/mL; if <LLOQ, then LLOQ/2 was assigned.
^^ 31 subjects (2.6%) had baseline GP ELISA ⩾ 200 EU/mL and were excluded from Per-Protocol analysis.
Source: Adapted from Table 11-4 in the CSR of V920-012.

Since the evaluation of clinical efficacy and immunogenicity has never been done in a same study, it is not possible to define a correlate of protection (immunity). Thus, interpretation of the above immunogenicity results could not be done at this time.

6.2.12 Safety Analyses

The primary population for safety analysis was the All Subjects as Treated (ASaT) population. The ASaT population consisted of all randomized subjects who received a dose of study vaccination with safety follow-up. (3 lots combined: High Dose: Placebo = 791: 260: 133)

From Day 1 to Month 6, 18 (2.3%) subjects in the combined Lots A, B, and C group (including 2 deaths) and 3 (1.1%) subjects in the High Dose group reported SAEs, while no SAEs were reported in the placebo group. None of the SAEs were determined (by the applicant) to be related to the study vaccine.

From Day 1 to Month 6, 44 (5.5%) subjects in the combined Lots A, B, and C group (including 2 deaths) and 9 (3.4%) subjects in the High Dose group were discontinued, while 3 (2.3%) subjects who received placebo were discontinued. No subjects discontinued from the trial due to a non-fatal AE.

One subject in the Lot A group experienced an SAE of craniocerebral injury due to a fall at Day 110 and died at Day 164. Another subject in the Lot B group experienced an SAE of hepatic failure due to alcoholism at Day 30 and died at Day 116. Both were determined (by the applicant) to be not-related to the study vaccine.

For the analyses of secondary safety endpoints, please refer to this section in the clinical reviewer's review.

6.2.13 Subgroup Analyses of the Immunogenicity Endpoint

Overall, immunogenicity of V920 Ebola vaccine was generally comparable in subgroups based on age (18-45, 46-65 years), gender (female, male) and race (non-White, White).

6.3 V920-009

Title of the study: "Partnership for Research on Ebola Vaccines in Liberia (PREVAIL)"

Study start date: 2/2/2015
Study completion date: 5/12/2016

6.3.1 Objectives

This study was originally designed to evaluate the safety and efficacy of V920 Ebola vaccine and ChAd3 Ebola vaccine. However, efficacy was not evaluated due to declining incidence of EVD in Liberia. It was later modified to evaluate the safety and immunogenicity. This review covers the safety and immunogenicity (instead of efficacy) of V920 Ebola vaccine.

The primary objective of this study was to evaluate the safety of V920 with respect to SAEs through 12 months post-vaccination.

The secondary objectives were:

(1) to estimate the geometric mean titers (GMTs) of antibodies as measured by GP-ELISA at Months 1, 6, and 12 post-vaccination.
(2) to estimate the GMTs of neutralizing antibodies measured by plaque reduction neutralization test (PRNT) at Months 1, 6, and 12 post-vaccination.

6.3.2 Design Overview

V920-009 was originally designed as a Phase 2/3 randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of two Ebola vaccine candidates (V920 and ChAd3) in subjects 18 years of age and older in Liberia. The initial target of recruiting 600 subjects into the Phase 2 portion of the study was finished in March of 2015, and the Phase 2 portion was later expanded to recruit a total of 1500 subjects with follow-up for 12 months to obtain more safety and immunogenicity data.

Subjects were randomized, in a 2:1:2:1 ratio, to V920 (n=500): placebo (n=250): ChAd3 (n=500): placebo (n=250). Due to the low incidence of EVD in Liberia at that time, recruitment ended on April of 2015, *before any subjects were enrolled in the Phase 3 portion of the trial*. Overall, 1500 subjects were screened and randomized in the trial: 500 subjects each in the V920, ChAd3-EBO Z, and two placebo groups combined.

Clinical efficacy was not evaluated for either vaccine candidate due to the declining incidence of EVD in Liberia at the time of recruitment. Instead immunogenicity analyses through Month 12 post-vaccination with respect to GP-ELISA and PRNT were performed.

6.3.3 Population

Of the 500 subjects who received V920, 477 subjects had at least one specimen available for immunogenicity testing using the validated GP-ELISA through Month 12 post-vaccination and were included in the Full Analysis Set (FAS) immunogenicity populations. Data for subjects who received the ChAd3 vaccine or placebo were not tested using the validated assays.

The All Subjects as Treated (ASaT) population was used for the safety analyses. The ASaT population consisted of all randomized subjects who received a single dose of V920 (n=500) or two placebo groups combined (n=500).

6.3.4 Study Treatments or Agents Mandated by the Protocol

V920: V920 rVSV-ZEBOV (a recombinant, replication competent vesicular stomatitis virus-based vaccine expressing a surface glycoprotein of Zaire Ebolavirus). The vaccine dose of $2x10^7$ pfu (nominal dose) was injected intramuscularly (IM) as a single dose of 1 mL in the deltoid muscle.

Placebo for V920: Normal saline was injected intramuscularly (IM) as a single dose of 1 mL in the deltoid muscle.

ChAd3: ChAd3-EBO Z (replication deficient investigational EBOV vaccine encoded by Chimpanzee-derived adenovirus) was injected intramuscularly (IM) as a single dose of 2 mL in the deltoid muscle.

Placebo for ChAd3: Normal saline was injected intramuscularly (IM) as a single dose of 2 mL in the deltoid muscle.

6.3.6 Sites and centers

This trial was conducted at 1 trial center at Redemption Hospital in Monrovia, Liberia.

6.3.7 Surveillance/Monitoring

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

6.3.8 Endpoints and Criteria for Study Success

Immunogenicity endpoints: The immunogenicity endpoints were the antibody titers as measured by GP-ELISA, and the antibody titers as measured by plaque reduction neutralization test (PRNT) at Months 1, 6, and 12 post-vaccination. No hypothesis was tested based on these endpoints.

Safety endpoints: The primary safety endpoint was SAEs during the first 30 days of vaccination. The secondary safety endpoint was SAEs through 12 months post-vaccination. No hypothesis was tested based on these endpoints.

6.3.9 Statistical Considerations and Statistical Analysis Plan

No hypothesis was tested in this study. Safety and immunogenicity data were summarized descriptively.

6.3.10 Immunogenicity Analyses

Immunogenicity analyses was only for the subjects who received the V920 Ebola vaccine. Data for subjects who received the ChAd3 vaccine or placebo were not tested with the validated assays.

GMTs (with 95% CI) of antibodies as measured by GP-ELISA at Month 1, 6, and 12 post-vaccination were estimated based on the GP-ELISA FAS Immunogenicity Population, and the results are presented in Table 13:

Table 13^: GMTs with 95% CI for GP-ELISA
[FAS Immunogenicity Population]

Baseline^^ (n=464)	Month 1 (n=475)	Month 6 (n=477)	Month 12 (n=475)
118 (108, 129)	995 (915, 1081)	712 (659, 769)	661 (613, 713)

^LLOQ for GP-ELISA was 36.11 EU/mL; if <LLOQ, then LLOQ/2 was assigned.
^^ Ninety-seven (20.9%) of 464 subjects tested had a baseline GP-ELISA ⩾200 EU/ml.
Source: Adapted from Table 2.7.3: 8 in the summary of clinical efficacy.

Percentages of subjects with 2-fold increase from baseline titer and ≥200 EU/mL are shown in Table 14 with 95% CI at Months 1, 6, and 12.

Table 14: Percentage (with 95% CI) of subjects with 2-fold increase from baseline titer and ≥200 EU/mL
[FAS Immunogenicity Population]

Month 1	Month 6	Month 12
90.0% (86.9, 92.6)	83.2% (79.5, 86.5)	80.1% (76.2, 83.7)

Source: Adapted from Table 2.7.3: 10 in the summary of clinical efficacy.

Since the evaluation of clinical efficacy and immunogenicity has never been done in a same study, it is not possible to define a correlate of protection (immunity). Thus, interpretation of the above immunogenicity results could not be done at this time.

6.3.12 Safety Analyses

The All Subjects as Treated (ASaT) population was used for the safety analyses. The ASaT population consisted of all randomized subjects who received a single dose of V920 (n=500) or two placebo groups combined (n=500).

A total of 47 (9.4%) subjects of the 500 vaccinated with V920 experienced SAEs (including 5 deaths), while 59 (11.8%) subjects of the 500 received placebo (1 mL and 2 mL groups combined) experienced SAEs (including 6 deaths) from Day 1 to Year 1. None of the SAEs were determined (by the applicant) to be related to the study vaccine.

A total of 14 (2.8%) subjects (including 5 deaths) in the V920 group and 13 (2.6%) subjects (including 6 deaths) in the placebo group were discontinued from Day 1 to Year 1. No subjects discontinued from the trial due to a non-fatal AE.

6.4 V920-011

Title of the study: "[rVSVΔG-ZEBOV] Ebola Prevention Vaccine Evaluation in Sierra Leone; STRIVE (Sierra Leone Trial to Introduce a Vaccine against Ebola)"

Study start date: 4/9/2015
Study completion date: 11/8/2016

6.4.1 Objectives

This study was originally designed to evaluate the safety and efficacy of V920 Ebola vaccine. However, efficacy was not evaluated due to declining incidence of EVD in Sierra Leone. It was later modified to evaluate the safety and immunogenicity. This review covers the safety and immunogenicity (instead of efficacy) of V920 Ebola vaccine.

The primary objective of this study was to evaluate the safety of V920 with respect to SAEs during the first 6 months of vaccination.

The secondary objectives were:

(1) to estimate the geometric mean titers (GMTs) of antibodies as measured by GP-ELISA at Months 1, 6, and 9-12 post-vaccination among immunogenicity sub-study population.
(2) to estimate the GMTs of neutralizing antibodies measured by plaque reduction neutralization test (PRNT) at Months 1, 6, and 9-12 post-vaccination among immunogenicity sub-study population.
(3) to evaluate solicited injection-site and systemic Adverse Events (AEs) through Day 28 among safety sub-study population.

6.4.2 Design Overview

V920-011 was originally designed as a Phase 2/3 randomized, open-label trial in Sierra Leone to evaluate the safety and efficacy of V920 in a population of at-risk healthcare workers and Ebola front-line workers. Eligible subjects were enrolled and individually randomized to either the Immediate Vaccination group or the Deferred Vaccination group. Subjects in the Immediate Vaccination group received vaccination within 7 days of randomization and subjects in the Deferred Vaccination group received vaccination during 18 to 24 weeks after randomization. All subjects received a single nominal V920 dose of 2×10^7 pfu and were followed for 6 months post-vaccination for safety and EVD.

Overall, 8,651 subjects were randomized with valid consent in a 1:1 ratio (Immediate: Delayed = 4319: 4332). Of these subjects, 7,998 actually received study vaccination. A total of 528 subjects (all from the Immediate Vaccination group) were randomly selected for participation in the immunogenicity sub-study.

6.4.3 Population

The primary safety analysis population consisted of all vaccinated subjects in the Immediate vaccination arm and all subjects in the Deferred vaccination arm, with at least one documented safety assessment in the follow-up period (through Month 6).

A total of 528 subjects (*all from the Immediate Vaccination group* (n=4319)) were randomly selected for participation in the immunogenicity sub-study. However, immunogenicity data are summarized for 508 subjects who were vaccinated and provided sample(s) for the assessment of immunogenicity. Among the 508 vaccinated and provided samples for the immunogenicity, 506 (504) subjects had at least one GP-ELISA (PRNT) result for the samples collected within the allowed time windows and were included in the GP-ELISA (PRNT) FAS population.

A safety sub-study was conducted in this trial. The safety sub-study was a subset of the overall population in each vaccination arm (Immediate and Deferred) who were eligible for participation in the trial and consented to be in the safety sub-study (Immediate: Deferred = 225: 224). Detailed safety follow-up for the solicited injection-site and

systemic Adverse Events (AEs) from Days 0 to 28 post-vaccination (Immediate Vaccinate group) or post-enrollment (Deferred Vaccination group) was performed among the safety sub-study population.

6.4.4 Study Treatments or Agents Mandated by the Protocol

Immediate Vaccination Group: rVSV-ZEBOV (a recombinant, replication competent vesicular stomatitis virus-based vaccine expressing a surface glycoprotein of Zaire Ebolavirus). The vaccine dose of $2x10^7$ pfu (nominal dose) was injected intramuscularly (IM) as a single dose of 1 mL in the deltoid muscle within 7 days of randomization.

Deferred Vaccination Group: rVSV-ZEBOV (a recombinant, replication competent vesicular stomatitis virus-based vaccine expressing a surface glycoprotein of Zaire Ebolavirus). The vaccine dose of $2x10^7$ pfu (nominal dose) was injected intramuscularly (IM) as a single dose of 1 mL in the deltoid muscle at the end of 18-24 weeks follow-up period.

6.4.6 Sites and centers

A total of 7 trial enrollment and vaccination centers were set up in 5 districts in Sierra Leone.

6.4.7 Surveillance/Monitoring

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

6.4.8 Endpoints and Criteria for Study Success

Immunogenicity endpoints: The immunogenicity endpoints were the antibody titers as measured by GP-ELISA, and the antibody titers as measured by plaque reduction neutralization test (PRNT) at Months 1, 6, and 9-12 post-vaccination. No hypothesis was tested based on these endpoints.

Safety endpoints: The primary safety endpoint was SAEs during the first 6 months of vaccination. The secondary safety endpoint was solicited injection-site and systemic Adverse Events (AEs) through Day 28 among safety sub-study population.

6.4.9 Statistical Considerations and Statistical Analysis Plan

No hypothesis was tested in this study. Safety and immunogenicity data were summarized descriptively.

6.4.10 Immunogenicity Analyses

GMTs (with 95% CI) of antibodies as measured by GP-ELISA at Months 1, 6, and 9-12 post-vaccination were estimated based on the GP-ELISA FAS Immunogenicity Population (see section 6.4.3), and the results are in Table 15:

Table 15^: GMTs with 95% CI for GP-ELISA
[FAS Immunogenicity Population]

Baseline^ (n=506)	Month 1 (n=443)	Month 6 (n=383)	Month 9-12 (n=396)
93 (85, 101)	964 (879, 1058)	752 (691, 818)	761 (698, 830)

^LLOQ for GP-ELISA was 36.11 EU/mL; if <LLOQ, then LLOQ/2 was assigned.
^^ Seventy-six (15.0%) of the 506 subjects tested had a baseline GP-ELISA ⩾200 EU/ml
Source: Adapted from Table 2.7.3: 15 in the summary of clinical efficacy.

Percentages of subjects with 2-fold increase from baseline GP-ELISA titer and ≥200 EU/mL are shown in Table 16 with 95% CI at Months 1, 6, and 9-12.

Table 16: Percentage (with 95% CI) of subjects with 2-fold increase from baseline titer and ≥200 EU/mL
[FAS Immunogenicity Population]

Month 1	Month 6	Month 9-12
90.0% (86.8, 92.7)	89.5% (86.0, 92.4)	87.8% (84.1, 90.9)

Source: Adapted from Table 2.7.3: 17 in the summary of clinical efficacy.

Since the evaluation of clinical efficacy and immunogenicity has never been done in a same study, it is not possible to define a correlate of protection (immunity). Thus, interpretation of the above immunogenicity results could not be done at this time.

6.4.12 Safety Analyses

The primary safety analysis population consisted of all vaccinated subjects in the Immediate vaccination arm and all subjects in the Deferred vaccination arm, with at least one documented safety assessment in the follow-up period (through Month 6).

A total of 55 (1.3%) subjects among the 4165 vaccinees in the immediate vaccination group experienced SAEs (including 8 deaths), while 35 (0.8%) subjects among the 4332 subjects assigned to the deferred vaccination group experienced SAEs (including 6 deaths) before they received vaccination (18-24 weeks after enrollment). None of the SAEs were determined (by the applicant) to be related to the study vaccine.

A total of 218 (5.0%) subjects (including 8 deaths, 152 lost-to-follow-up) in the immediate vaccination group and 50 (1.2%) subjects (including 6 deaths, 32 lost-to-follow-up) in the deferred vaccination group were discontinued before they received vaccination (18-24 after enrollment). No subjects were claimed to be discontinued from the trial due to a non-fatal AE. However, the imbalance in numbers of lost-to-follow-up between the two groups (Immediate: Deferred = 152 (3.5%): 32 (0.7%)) may be a concern. The applicant did not provide the reasons of lost-to-follow-up. One possible explanation could be that since it is an open-label study, once the subjects in the

immediate vaccination group got vaccinated, they might lose interest in the study participation, while the subjects in the deferred vaccination group were expected to maintain interest in the study participation until they got vaccinated 18-24 weeks after enrollment.

7. Integrated Overview of Efficacy and Immunogenicity

Among 4 studies describe in this review, the clinical efficacy was evaluated only in V920-010, and lot consistency was evaluated only in V920-012.

Immunogenicity of V920 Ebola vaccine was investigated in studies V920-009, V920-011, and V920-12. Across these three studies, percentages of subjects with 2-fold increase from baseline titer and ≥200 EU/mL (GP-ELISA) at 1 month from vaccination range from 90.0% up to 97.8% with lower bounds of the 95% CIs ranging from 86.8% to 95.0%. At 6 months after vaccination, they range from 83.2% to 95.4% with lower bounds of the 95% CIs ranging from 79.5% to 91.7%. However, since the evaluation of clinical efficacy and immunogenicity has never been done in a same study, it is not possible to define a correlate of protection (immunity). Thus, interpretation of the immunogenicity results could not be done at this time.

8. Integrated Overview of Safety

In V920-010, among 5837 vaccinated subjects, 65 (1.1%) subjects experienced SAEs. Febrile reaction in one subject and anaphylaxis in another subject (both resolved later) were determined by the investigator to be related to the study vaccine. Influenza-like illness in one subject (resolved later) was determined to be possibly-related to the study vaccine.

In V920-009, V920-011 and V920-012, none of the SAEs were determined (by the applicant) to be related to the study vaccine.

For further discussion of safety overview, please refer to this section in the clinical reviewer's review.

10. Conclusions

1. Clinical efficacy of V920 Ebola vaccine was evaluated only in V920-010 (Guinea Ring Vaccination Study). Since there was no EVD observed in the immediate vaccination arm after Day 10, the point estimate of VE is 100% regardless of the statistical model. The lower bound of the 95% CI of VE is 15.5% based on the estimation at the ring level, while it is 63.5% based on the applicant's model. The VE point estimate of 100% should be interpreted with caution because of the

potential behavioral modification among the subjects in the immediate vaccination arm due to the medical study team's stay during Day 0 to Day 21 as described in section 6.1.10.

2. Lot consistency was evaluated in V920-012. Lot consistency between the three lots was demonstrated based on pre-specified criterion. The criterion was that for each of the three pair-wise comparisons between the lots, the lower bound of the 95% CI of the GMT ratio (GP-ELISA) between the groups being compared should be greater than 0.67 and the upper bound should be less than 1.5.

3. Immunogenicity of V920 Ebola vaccine was investigated in studies V920-009, V920-011, and V920-12. Across these three studies, percentages of subjects with 2-fold increase from baseline titer and ⩾200 EU/mL (GP-ELISA) at 1 month after vaccination range from 90.0% up to 97.8% with lower bounds of the 95% CIs ranging from 86.8% to 95.0%. At 6 months after vaccination, the percentages range from 83.2% to 95.4% with lower bounds of the 95% CIs ranging from 79.5% to 91.7%. However, since the evaluation of clinical efficacy and immunogenicity has never been done in a same study, it is not possible to define a correlate of protection (immunity). Thus, a statistical interpretation of the immunogenicity results can not be provided at this time.

4. In V920-010, among 5837 vaccinated subjects, there were 2 SAEs determined to be related to the study vaccine, and 1 SAE determined to be possibly-related to the study vaccine. In V920-009, V920-011 and V920-012, none of the SAEs were determined (by the applicant) to be related to the study vaccine.

5. There are notable constraints to interpreting the clinical evidence presented in this BLA. Specifically, the declining incidence of EVD over the period of late-phase development of the V920 Ebola vaccine along with the lack of a known correlate of protection limit the strength of evidence of effectiveness available in the application. However, within these constraints, I believe the statistical evidence presented in the BLA supports the effectiveness and safety of the V920 Ebola vaccine in the proposed indication and recommend it be approved.