BLA Clinical Review Memorandum

Application Type	Original BLA
STN	125690
CBER Received Date	October 24, 2018 (initial submission, rolling BLA); July 15, 2019 (clock start)
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Division / Office	Division of Vaccines and Related Product Applications/Office of Vaccines
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Rebecca Reindel, MD
Review Completion Date / Stamped Date	December 19, 2019
Supervisory Concurrence	for Andrea Hulse, MD Chief 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 18 years of age and older
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	Adverse event
AESI	Adverse events of special interest
ASaT	All subjects as treated
BIMO	Bioresearch monitoring
BLA	Biologics license application
BPCA	Best Pharmaceuticals for Children Act
CBER	Center for Biologics Evaluation and Research
CCC	Contacts and contacts of contacts
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMC	Chemistry, manufacturing, and controls
CRF	Case report form
CSR	Clinical study report
DSMB	Data Safety Monitoring Board
eCTD	electronic Common Technical Document
ELISA	Enzyme-Linked Immunosorbent Assay
EML	European Mobile Laboratory
ES	Executive Summary
ETC	Ebola treatment center
ETU	Ebola treatment unit
EVD	Ebola virus disease
FAS	Full analysis set
GCP	Good Clinical Practice
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
HCW	Health care worker
ICF	Informed consent form
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IM	Intramuscular
IR	Information request
IRB	Institutional review board
ISE	integrated summary of efficacy
ISS	integrated summary of safety
ITT	intent-to-treat
LLOD	Lower limit of detection
LLOQ	Lower limit of quantitation
LMP	Last menstrual period
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MOH	Ministry of Health
NHP	Non-human primates
OBE	Office of Biostatistics and Epidemiology
PBS	Phosphate buffered saline

PD	Pharmacodynamics
PeRC	Pediatric Review Committee (CBER)
PI	Package insert
PK	Pharmacokinetics
PMC	Postmarketing commitment
PMR	Postmarketing requirement
PP	Per-protocol
PREA	Pediatric Research Equity Act
PRNT	Plaque reduction neutralization test
PSP	Pediatric Study Plan
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study data tabulation model
VE	Vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Committee
VRC	Vaccine report card
VSV	Vesicular Stomatitis Virus
WBC	White blood cell
WHO	World Health Organization
ZEBOV-GP	*Zaire ebolavirus* Kikwit strain glycoprotein

1. Executive Summary

The Applicant, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., (Merck), has submitted a Biologics License Application (BLA) for Ebola Zaire Vaccine to support licensure of V920, a recombinant viral vaccine consisting of a recombinant Vesicular Stomatitis Virus (VSV) with the gene for the *Zaire ebolavirus* Kikwit strain glycoprotein (ZEBOV-GP) replacing the gene for the native VSV glycoprotein. V920 is indicated for the prevention of disease caused by *Zaire ebolavirus* in individuals 18 years of age and older.

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

The primary prespecified efficacy outcome was confirmed EVD, defined as: 1) any probable or suspected case for which an associated blood sample was laboratory-confirmed as positive for EVD; or 2) any deceased individual with probable EVD, from which a post-mortem sample taken within 48 hours after death was laboratory-confirmed as positive for EVD. The analysis period for assessing efficacy and the populations selected for the primary efficacy analysis were not prespecified. In amendments to the Statistical Analysis Plan, the analysis period was defined as events that occur between D and 21+D days. The per protocol primary analysis value for D was not fixed and defaulted to the intent-to-treat analysis where D=10. Based on regulatory feedback, the study population for the primary efficacy analysis included only those subjects in the delayed vaccination clusters who consented at Day 0 to control for comparison group bias by addressing efficacy among prospectively consenting individuals.

The population for the primary efficacy analysis (all vaccinated subjects in the immediate clusters versus all subjects who were eligible and consented at Day 0 in the delayed clusters) included 3,537 subjects ≥18 years of age who were considered contacts and contacts of contacts of an index case with laboratory confirmed EVD. Of these, 2,108 were included in 51 immediate vaccination clusters, and 1,429 were included in 46 delayed vaccination clusters. In the primary efficacy analysis, no cases of confirmed EVD were observed in the immediate clusters and a total of ten confirmed EVD cases were observed in four rings in the delayed clusters, resulting in a point estimate of vaccine efficacy (VE) of 100% (95% CI: 63.5 to 100%, p=0.0471). Cases of EVD that occurred between Day 10 and 31 post-randomization of the cluster were included in the analysis. Cases of EVD reported between randomization of the cluster and Day 10 were censored to maintain the comparability of the populations with respect to exposure to the index case. Cases occurring after Day 31 were also censored to account for vaccination on Day 21 in the delayed clusters. There were no EVD cases after 32 days post-randomization. Additional efficacy analyses, some of which were not prespecified, were conducted to assess potential sources of bias and were generally comparable to the primary analysis.

Safety: Overall, a total of 15,997 adults subjects received V920 in 12 clinical studies, including 15,399 subjects who received a dose of ≥2 x 10^7 pfu. In the seven blinded and placebo-controlled clinical studies, 1,712 subjects received a dose of V920 ≥2 x 10^7 pfu and 459 subjects received a dose of V920 <2 x 10^7 pfu. In the five open-label clinical studies 13,687 adult subjects received a dose received a dose of V920 ≥2 x 10^7 pfu and 139 subjects received a dose of V920 <2 x 10^7 pfu.

The 12 clinical studies in the development program included eight Phase 1 studies (including five blinded and placebo-controlled studies and three open-label studies), and four Phase 2/3 studies (including two blinded and placebo-controlled studies [V920-009 and V920-012] and two open-label studies [V920-010 and V920-011]). As the studies included in the BLA were conducted by multiple sponsors, safety data collection methods varied between studies. Due to these differences across studies, pooled safety data was limited to serious adverse events (SAEs) reported in the blinded studies, including V920-001, V920-002, V920-003, V920-004, V920-005, V920-009, and V920-012.

In blinded studies, the following general safety findings were reported:

- Injection site pain was the most commonly reported solicited local event and was reported by a higher proportion of subjects after V920 compared to placebo. Across the blinded Phase 1 studies, pain (captured as injection site pain, arm pain, or local tenderness) was reported by 59.6% to 100% of subjects in study groups that received V920 doses ≥2 x 10^7 pfu, compared to 7.4% to 33% of placebo recipients. Injection site erythema and swelling were reported by 2.1% to 20% and 2.1% to 10% of subjects in study groups that received V920 doses ≥2 x 10^7 pfu, respectively, compared to 0% of placebo recipients. In V920-009, injection site pain was reported by 34.0% of V920 recipients and 11.2% of placebo recipients and local reactions were reported by 1.8% of V920 recipients and 0.8% of placebo recipients. In V920-012, injection site pain was reported by 69.5% of V920 recipients (Combined Lots and High Dose groups) and 12.8% of placebo recipients; injection site erythema was reported by 11.9% of V920 recipients in and 1.5% of placebo recipients; and injection site swelling was reported by 16.5% of V920 recipients and 3.0% of placebo recipients. Severe solicited local events were infrequent (~3% of subjects in V920-012 and 0% in V920-009).
- In the Phase 1 blinded studies, a higher proportion of subjects in the study groups that received ≥2 x 10^7 pfu V920 reported solicited systemic events (70% to 100%) compared to subjects in the placebo group (33.3 to 100%) through Day 14. The proportions of subjects reporting each solicited systemic event varied between the Phase 1 blinded studies but were generally higher for each event after V920 compared to placebo. The following solicited systemic events were the most commonly reported by subjects who received ≥2 x 10^7 pfu V920: chills (27.7% to 70%), fatigue (38.3% to 90%), headache (43.8% to 80%), myalgia (33.3% to 100%), objective fever (12.5% to 50%), and subjective fever (29.2% to 80%). Severe solicited systemic events reported by subjects who received ≥2 x 10^7 pfu V920 included: chills, fatigue, headache, myalgia, sweats, and subjective or objective fever. Severe events were reported at most by one to two subjects per dosing group. In V920-009, a higher proportion of subjects in the V920 group reported solicited systemic events (61.6%) compared to subjects in the placebo group (56.7%) through Day 28. The following solicited systemic events were the most commonly reported: fatigue (18.5% of V920 recipients compared to 13.4% of placebo recipients), pyrexia (34.3% of V920 recipients compared to 14.8% of placebo recipients), myalgia (32.5% of V920 recipients compared to 22.8% of placebo recipients), and headache (36.9% of V920 recipients compared to 23.2% of placebo recipients). No subject reported severe events.
- In some blinded studies, events of arthritis were reported by a higher proportion of subjects after V920 compared to placebo, including 23.5% of V920 recipients in a Phase 1 study (V920-005). Some subjects in this study reported severe and prolonged events (2 years post-vaccination) of arthritis. In some tested subjects with arthritis, vaccine virus RNA was detected in the synovial fluid. In V920-009, for the time period through Month 1, including the Week 2 subset data, the proportions of subjects reporting arthropathy, joint stiffness, and joint swelling were 0.6%, 0.4%, and 0.4%, respectively, after V920 and 0.2%, 0.2%, and 0.4%, respectively, after placebo. In V920-012, solicited events of arthritis were reported only in the Combined Lots and High Dose groups (4.9% and 4.6% of subjects, respectively), and were not reported after placebo.
- Across the two blinded studies that provide the most data for skin and mucosal lesions (V920-009 and V920-012), the proportions of subjects reporting solicited

skin-related events were generally comparable between the V920 (3.6% to 3.8%) and placebo (1.5% to 3.2%) groups, although vesicular lesions were observed only after V920 in V920-012. In V920-004 and V920-005, the proportions of subjects with rash after V920 were reported by 8.4% and 25% of subjects who received ≥2 x 107 pfu/dose V920, respectively, compared to 3.2% and 7.7% of placebo recipients, respectively. In some tested subjects, vaccine virus RNA was detected in vesicular fluid or skin biopsies. In V920-009, solicited events of mouth ulceration were reported by 2.6% of subjects after V920 and 2.6% of subjects after placebo.

- Decreases in white blood cell (WBC), lymphocyte, and neutrophil count were observed more frequently after V920 than placebo.
- Across blinded placebo-controlled studies in the clinical development program, fatal SAEs were reported for six of 766 placebo recipients (0.8%) in the ISS dataset compared to eight of 2,171 V920 recipients (0.4%). None of the deaths were attributed to vaccination. No clustering of deaths was noted, and no deaths were considered vaccine-related by the investigators.
- In the integrated analysis of SAEs across blinded studies in the clinical development program, SAEs were reported by a higher proportion of subjects after placebo (1.4%) compared to V920 (0.4% overall and 0.5% at doses ≥2 x 10^7 pfu/mL) in the first 28 days after vaccination. In the Day 1 to Day 180 time period, SAEs were reported by 6.3% of placebo recipients and 2.6% of V920 recipients (3.2% of subjects who received a dose of ≥2 x 10^7 pfu). Of the 1,712 V920 recipients included in the integrated safety analysis who received ≥2 x 10^7 pfu V920, the only MedDRA Preferred Term (PT) reported by more than three subjects was malaria.

Other safety findings included:

- Related SAEs were reported in V920-010 and included two events of anaphylaxis, pyrexia, influenza-like illness, infection, and febrile reaction.
- Imbalances in some SAEs, including neurovascular events, were noted in some studies, although the number of subjects reporting these SAEs was small.
- In the open-label Phase 2/3 studies, fatal SAEs were reported for 18 vaccinated subjects in V920-010 during the 84 day follow up period. In V920-011, 25 subjects (0.2%) experienced SAEs that resulted in death. During the 6-month follow-up period, eight subjects (0.2%) in the Immediate Vaccination group, 11 subjects (0.3%) in the Deferred-Crossover group, and six subjects (0.1%) in the Deferred Vaccination group died, including one subject who died during post-6 month follow-up. None of the deaths were considered related to vaccination.

Consultations: This submission is subject to the Pediatric Research Equity Act (PREA). FDA's Pediatric Review Committee (PeRC) and CBER agreed with the Applicant's request for a waiver of pediatric assessments for children from birth through 11 months of age as the studies are impossible or highly impracticable (e.g. the number of pediatric patients is so small or is geographically dispersed) (section 505B(a)(5)(B)(i)). The PeRC and CBER agreed with the Applicant's request for a deferral of the pediatric assessment for children 12 months through 17 years of age as the drug or biological product is ready for approval for use in adults before pediatric studies are complete (section 505B(a)(4)(A)(i)(I)).

Pharmacovigilance: The core Risk Management Plan includes viral shedding/secondary transmission to close contacts, particularly immunocompromised hosts, as an important potential risk; exposure during pregnancy, lactation, and in HIV-infected individuals as missing information; and does not include any important identified risks.

The potential risk of "viral shedding/secondary transmission to close contacts, particularly immunocompromised hosts" is adequately addressed with routine pharmacovigilance and that missing information on "exposure during pregnancy," "exposure during lactation," and "exposure in HIV-infected individuals" will be collected in ongoing studies, for which CBER will request the final study reports. Data regarding the potential risks of arthritis and safety and reduced efficacy in immunocompromised hosts will be available for analysis through routine pharmacovigilance.

Conclusions: Data submitted to the BLA establishes a substantial likelihood of benefit for the prevention of disease caused by Zaire ebolavirus in individuals 18 years of age and older. Risks of V920 include anaphylaxis, local and systemic reactogenicity, including infrequent severe reactogenicity events, events of arthritis, and potential transmission of vaccine virus to unvaccinated contacts. Comparison of safety data across studies was limited by variability in the collection and reporting of safety data and limited numbers of subjects in the blinded study populations. In the context of the high morbidity and mortality associated with EVD, the benefit-risk profile of V920 supports approval in individuals ≥ 18 years of age. The clinical reviewer recommends approval of V920 for the prevention of disease caused by *Zaire ebolavirus* in individuals 18 years of age and older

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Overall, a total of 15,997 adults subjects received V920 in 12 clinical studies, including 15,399 subjects who received a dose of ≥2 x 10^7 pfu. In the seven blinded and placebo-controlled clinical studies, 1,712 subjects received a dose of V920 ≥2 x 10^7 pfu and 459 subjects received a dose of V920 <2 x 10^7 pfu. In the five open-label clinical studies 13,687 adult subjects received a dose received a dose of V920 ≥2 x 10^7 pfu and 139 subjects received a dose of V920 <2 x 10^7 pfu.

Phase 1 Study Demographics
The following table provides demographic subgroup information for the blinded Phase 1 studies.

Table 1 Demographic subgroup information for blinded Phase 1 studies

	Blinded Phase 1 studies N= 745 n (%)
Male	401 (53.8)
Female	344 (46.2)
<18 YOA	0 (0)
18-45 YOA	536 (71.9)
46-65 YOA	209 (28.1)
Black or African American	203 (27.2)
Other	27 (3.6)
White	513 (68.9)
Hispanic or Latino	86 (11.5)

	Blinded Phase 1 studies N= 745 n (%)
Not Hispanic or Latino	659 (88.5)

Blinded Phase 1 studies include V920-001, V920-002, V920-003, V920-004, V920-005, including 459 subjects who received <2 x 10^7 pfu V920
Source: Original BLA 125690/1, Risk Management Plan, pg. 13 and 20, Tables SIII.2.1 and SIII.4.1

Phase 2/3 Study Demographics
The following table provides demographic subgroup information for each of the Phase 2/3 studies.

Table 2 Demographic subgroup information for Phase 2/3 studies

	V920-009 N=1000 n (%)	**V920-010 N=3586* n (%)**	**V920-011 N=8651 n (%)**	**V920-012 N=1197 n (%)**
Male	636 (63.6)	2517 (70.2)	5244 (61)	560 (46.8)
Female	364 (36.4)	1068 (29.7)	3407 (39)	637 (53.2)
Unknown	0 (0)	1 (<0.1)	0 (0)	0 (0)
<18 YOA	2 (0.2)	0 (0)	0 (0)	0 (0)
18-64 YOA	981 (98.1)	3221 (89.8)	8621 (99.7)	1186 (99.1)
≥65 YOA	17 (1.7)	365 (10.2)	30 (0.3)	11 (0.9)
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)	5 (0.4)
Asian	0 (0)	0 (0)	3 (0.03)	9 (0.8)
Black or African American	100 (100)	100 (0)	8637 (99.8)	350 (29.2)
Multiple	0 (0)	0 (0)	10 (0.1)	17 (1.4)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	0 (0)	3 (0.3)
White	0 (0)	0 (0)	1(0.01)	813 (67.2)
Hispanic or Latino	0 (0)	0 (0)	0 (0)	173 (14.5)
Not Hispanic or Latino	0 (0)	0 (0)	0 (0)	1020 (85.2)

YOA= years of age; Populations used for demographics: All randomized subjects in each study
*Numbers provided for V920-010 includes all consented subjects in the immediate group and all subjects who were consented at Day 0 in the delayed group
Source: Original BLA 125690/1; Summary of Clinical Safety, pages 49- 52, V920-010 Clinical Study Report, page 77, and Clinical Study Report V920-011, p.111 and ADSL dataset

Reviewer's comment: A small discrepancy in the number of subjects ≥65 in V920-010 was observed between the SDTM datasets (n= 365) and the V920-010 study report (n= 364).

In V920-010, the population for the primary efficacy analyses included all vaccinated subjects in the immediate group and all subjects who were eligible and consented at Day 0 in the delayed group. However, the population for safety analysis included eligible, consented, and vaccinated subjects, both randomized and non-randomized (n= 5643 adults and 194 children). Therefore, the demographics of the safety population are different for V920-010. Of the 5643 vaccinated adults, 3816 were male (67.6%), 1827 were female (32.4%), and one was unknown (<0.1%). By age group, 497 subjects were ≥65 years of age (8.8%) and 5146 were 18 through 64 years of age (91.2%).

Efficacy
V920-010 was conducted in Guinea and served as the primary basis for demonstration of effectiveness. All subjects were categorized by race as Black or African American. Therefore, sub-analyses of efficacy were provided by age and sex on the populations

used in the primary efficacy analysis for V920-010 (vaccinated subjects in the immediate group and subjects who were consented at Day 0 in the delayed group).

Of the 2108 subjects in the immediate vaccination clusters, 70.4% were male, 29.6% were female, 76.7% were between 18 and 55 years of age, and 23.3% were >55 years of age. Of the 1429 subjects in the delayed vaccination clusters, 70.3% were male, 29.7% were female, 80.3% were between 18 and 55 years of age, and 19.7% were >55 years of age. Vaccine efficacy was 100% for all subgroups, with the following 95% CI for each subgroup: males (95% CI: 52.1, 100), females (95% CI: 30.4, 100), 18 to 55 years of age (95% CI: 49.9, 100), and >55 years of age (41.2, 100).

Reviewer's comment: The Applicant provided subgroup analyses of efficacy by sex and age in response to an IR. The age subgroup analyses were conducted using an age cutoff of 55 years of age, not ≥65 years of age. Due to small sample sizes, the 95% confidence intervals are wide in each subgroup. Of the 135 subjects ≥65 years of age in the deferred vaccination clusters who consented at Day 0, two had EVD; of the 230 subjects ≥65 years of age in the Immediate group, none had EVD. Meaningful differences in vaccine efficacy by sex and age were not detected, although the number of geriatric subjects was limited.

In the absence of efficacy data that allows comparison between racial and geographic groups, immunogenicity data from the Phase 3 immunogenicity studies can provide an overall comparison of humoral immune responses by geographic region. The following table summarizes the Month 1 immunogenicity data for each study for the GP-ELISA and the plaque reduction neutralization test (PRNT) assay by geometric mean titer (GMT) and geometric mean fold rise (GMFR).

Table 3 Summary of GP-ELISA and plaque reduction neutralization test (PRNT) assay geometric mean titer (GMT) and geometric mean fold rise (GMFR) by study

	V920-009 Liberia	**V920-011 Sierra Leone**	**V920-012 US/Europe**
GP-ELISA Month 1 GMT (n) [95% CI]	994.7 (475) [915.0, 1081.3]	964.3 (443) [878.7, 1058.3]	1262 (696) [1168.9, 1362.6]
GP-ELISA Month 1 GMFR (n) [95% CI]	8.5 (462) [7.7, 9.4]	10.7 (441) [9.6, 12.0]	64.2 (696) [59.3, 69.4]
PRNT Month 1 GMT (n) [95% CI]	116.8 (477) [106.0, 128.8]	116.0 (437) [105.7, 127.4]	202.1 (696) [187.9, 217.4]
PRNT Month 1 GMFR (n) [95% CI]	4.4 (428) [4.0, 4.8]	6.3 (376) [5.7, 7.0]	11.4 (696) [10.6, 12.3]

GMT= geometric mean titer; GMFR: geometric mean fold rise
Populations used for immunogenicity assessments: V920-009 Full Analysis Population; V920-011 Full Analysis Set Immunogenicity Population; and V920-012 Per protocol immunogenicity population (Combined Lots Group).
Source: Original BLA 125690/1, Summary of Clinical Efficacy, pages 47-49, 55-57, 62-63, 71, 79, 81, 87, and 89.

Reviewer's comment: In the absence of a known correlate of protection, the impact of any differences in immunogenicity data between racial subgroups on vaccine efficacy is unknown. Comparisons of each of the Phase 3 studies provides some insight into racial differences in immune response, as subjects in V920-009 and V920-011 were African and subjects in V920-12 were predominantly white subjects from North America and Europe (67.9% of subjects). However, it is important to note differences in specimen

processing (including gamma irradiation of African samples) between studies, potential variations in assay performance between studies, and differences in baseline seropositivity (15-20% in African studies compared to 2.6% US/Europe) confound direct comparisons of immunogenicity data across studies. Gamma irradiation of samples in V920-009 and V920-011 was conducted to reduce the potential risk of transmission of Ebola from study specimens to laboratory workers. In studies conducted by the Applicant, gamma irradiation has been demonstrated to result in an approximate 20% elevation in measured antibody response for negative clinical samples and an approximate 20% reduction in post-vaccination antibody response (1.21-fold decrease with 95% [CI = 1.15, 1.27-fold]) in the GP-ELISA, which may explain some of the difference in GP-ELISA GMTs between the African studies V920-009 and V920-011 and the US/European study V920-012.

Safety

Statistical analyses of common safety findings by sex, age, and race were not conducted for the blinded, placebo-controlled Phase 2/3 studies (V920-009 and V920-012). Due to differences in safety data collection procedures between studies, the pooling of safety data across blinded, placebo-controlled studies was limited to SAEs, including data from blinded Phase 1 studies. Descriptive analyses of safety data for the variables of sex, age, and race are presented below for V920-009 and V920-012.

Sex

In V920-009, injection site reactions were reported by 37.1% of male subjects after V920 compared to 28.9% of female subjects, most of which were injection site pain. Solicited systemic reactions were reported by 59.0% of male subjects after V920 compared to 33.9% of female subjects. Solicited events reported after V920 with a ≥5% difference between the proportions of female and male subjects included headache (43.5% of females and 33.0% of males) and myalgia (37.6% of females and 29.5% of males). Unsolicited events were reported by 26.5% of males and 23.0% of females after V920. The proportions of males and females reporting each unsolicited event PT were generally comparable. Serious adverse events were reported by 8.6% of male subjects and 10.7% of female subjects after V920, compared to 12.4% of male subjects and 10.7% of female subjects after placebo. With the exception of malaria, no SAE PT was reported by more than two male or female subjects, and with the exception of the Infections and infestations MedDRA System Organ Class (SOC), there were no more than two male or female subjects who reported events in any other SOC.

Reviewer's comment: Analyses of safety data by sex and age for V920-009 were provided by the Applicant in response to an IR.

In V920-012, adverse events were generally reported by a higher proportion of female subjects after V920 (both Combined Lots group and High Dose group) compared to male subjects, including injection site reactions (76.2% to 77.2% of females versus 62.8% to 67.7% of males), non-injection site reactions (64.6% to 71.4% of females versus 62.8% to 67.7% of males), vaccine-related adverse events (80.1% to 82.3% of females versus 77.0% to 77.5% of males), and serious adverse events (0% to 1% of females versus 0% to 0.5% of males).

Reviewer's comment: Across V920-009 and V920-012, differences in adverse events between male and female subjects were generally small. No safety concern specific to males or females was identified.

Age
V920-009 included 17 subjects ≥65 years of age, including six subjects in the V920 group and 11 subjects in the placebo group. Solicited local events were reported by 33.3% of V920 recipients ≥65 years of age and 34.0% of V920 recipients overall. Solicited systemic events were reported by 66.6% of V920 recipients ≥65 years of age and 61.6% of V920 recipients overall.

Solicited events reported after V920 with a ≥5% difference between the proportions of subjects >65 years of age and 18 through 65 years of age included myalgia, nausea, and pyrexia, which were reported by a higher proportion of subjects >65 years of age, and arthralgia, which was reported by a higher proportion of subjects 18 through 65 years of age. Unsolicited events were reported by 60.0% of subjects >65 years of age and 24.8% of subjects 18 through 65 years of age. Of the five subjects >65 years of age, three reported unsolicited events, including malaria, decreased appetite, malignant hypertension, and depression, all of which were SAEs except decreased appetite.

Reviewer's comment: In response to an IR, the Applicant provided analyses by age that categorized subjects 18 through 65 years of age and >65 years of age, although information in the Prescribing Information will address subjects ≥65 years of age. In the datasets for V920-009, there was only one subject 65 years of age enrolled in the study (V920 group). In the ADAE dataset, this subject reported mild events of cough and pyrexia.

The proportions of subjects >65 years of age reporting unsolicited and serious adverse events is higher than in the younger age cohort; however, the very small number of subjects >65 years of age confounds the comparison.

V920-012 included 11 subjects ≥65 years of age, including nine subjects in the Combined Lots group, one subject in the High Dose group, and 1 subject in the placebo group. All subjects were 65 years of age. Of the 10 V920 recipients ≥65 years of age, six (60.0%) reported injection site pain, compared to 70.4% and 72.3% of subjects overall in the Combined Lots and High Dose groups, overall. Of the systemic events reported by subjects 65 years of age, each was reported by two subjects at most. No serious adverse events were reported by subjects 65 years of age.

In a comparison of subjects 18 to 45 years of age to subjects 46 to 65 years of age in V920-012, injection site reactions, non-injection site reactions, vaccine related adverse events, and serious adverse events were reported by a similar proportion of subjects in each age group after V920. Events of arthralgia and arthritis were reported by a higher proportion of subjects in the 46 to 65 years of age category and females compared to the younger group after V920; however, the proportion of subjects reporting arthritis or arthralgia after placebo was comparable across the age and sex groups. Events of rash were reported by a lower proportion of subjects in the 46 to 65 years of age category compared to the younger group after V920; however, the proportion of subjects reporting rash after placebo was slightly higher in the 46 to 65-year old subjects.

Reviewer comments: Blinded, placebo-controlled data on vaccinated subjects ≥65 years is limited to 16 subjects, limiting a comprehensive understanding of the safety profile of the vaccine in this age group.

Race
In V920-012, race categories included White and Non-White race. Adverse events were generally reported by a higher proportion of White subjects after V920 (both Combined Lots group and High Dose group) compared to Non-White subjects, including injection site reactions (78.0% to 78.6% of White subjects versus 57.6% to 59.8% of Non-White subjects), non-injection site reactions (68.8% to 69.6% of White subjects versus 46.6% to 58.8% of Non-White subjects), and vaccine-related adverse events (84.6% to 86.3% of White subjects versus 66.3% to 74.1% of Non-White subjects). Serious adverse events were reported by similar proportions of White and Non-White subjects (0% to 0.4% of White subjects versus 0% to 1.6% of Non-White subjects). A higher proportion of White subjects reported arthritis and arthralgia compared to Non-White subjects after V920 and after placebo.

Reviewer comments: It is not clear why White subjects reported more adverse events compared to Non-White subjects. The pattern of the most commonly reported adverse events was comparable between the groups, although a higher proportion of White subjects reported specific events.

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 Ebola virus 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 (https://www.who.int/health-topics/ebola/#tab=tab_1, accessed September 25, 2019).

Epidemiology
Sporadic outbreaks of Ebola disease have been observed in Africa, including 20 known outbreaks between 1976 and 2014 (Malvy, 2019). A recent outbreak in Guinea, Liberia, and Sierra Leone resulted in 28,616 cases of Ebola virus disease (EVD) and 11,310 deaths between 2014 and 2016 (https://www.who.int/csr/disease/ebola/en/, accessed September 25, 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, Sierra Leone announced it was Ebola-free on March 7, 2016, and Guinea was declared Ebola-free in June 2016 (https://www.cdc.gov/vhf/ebola/history/2014-2016-outbreak/index.html). The strain circulating during the outbreak was an EBOV Makona variant (Kugelman, 2015).

As of the time of this review, an ongoing outbreak of Ebola in the Democratic Republic of Congo has resulted in over 3,000 EVD cases and over 2,000 deaths

(https://www.who.int/emergencies/diseases/ebola/drc-2019, accessed September 25, 2019).

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 and https://www.who.int/health-topics/ebola/#tab=tab_1, accessed September 25, 2019). In previous outbreaks, the case fatality rate ranged from 25% to 90% (https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease, accessed September 25, 2019); 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%. The case-fatality rate for the countries with the highest transmission rates were 28% in Sierra Leone, 45% in Liberia, and 66.7% in Guinea (Schultz, 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; and Clark, 2015).

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

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

There are no licensed preventive or therapeutic interventions indicated for Ebola virus disease, although experimental vaccines, monoclonal antibodies, and antivirals are undergoing clinical development. Currently, treatment of EVD is limited to supportive care, with symptom-based management of complications.

2.3 Safety and Efficacy of Pharmacologically Related Products

Ongoing clinical development programs are assessing the rVSVΔG vector, using inserts to elicit immune responses to RSV, HIV, and Lassa virus. 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 Ebola virus 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)

V920 is currently being administered in two Expanded Access Protocols initiated by the WHO in 2018 as part of a public health response to the currently ongoing Ebola

outbreak in the DRC (V920-EAP4 [Equateur province; completed; n= 3,481]) and V920-EAP5 [North Kivu, Rwanda, South Sudan, Uganda]). Between August 8, 2018 and December 10, 2019, a total of 256,381 individuals were vaccinated with V920 (https://www.who.int/publications-detail/ebola-virus-disease-democratic-republic-of-congo-external-situation-report-71-2019).

Breakthrough Ebola disease, defined as laboratory-confirmed Ebola disease (Zaire type) in a study subject with onset ≥10 days post-vaccination, was reported by 21 vaccinated subjects in the expanded access protocols (all in V920-EAP5), as of March 29, 2019. Of the 21 subjects, 15 subjects had Ebola disease confirmed with a positive Ebola virus PCR test and thus had confirmed breakthrough Ebola disease. Of the 15 subjects with confirmed breakthrough Ebola disease, 14 recovered and one had an unknown outcome at the time of the data lock for the safety update report. The time to onset of the cases ranged from 13 to 103 days after vaccination.

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

20 AUG 2014	IND 16131 was submitted by NewLink Genetics.
24 NOV 2014	Merck announced that they entered into a license agreement to develop, manufacture and distribute NewLink Genetics' investigational Ebola vaccine candidate.
14 JAN 2015	A **Type B** meeting was held with Merck. Key discussions and responses included: CBER's suggestion that the clinical studies use the same validated assay platform and method for comparison of results across studies, and that a Phase 2 study should be performed to evaluate safety in African populations with the final vaccine dose selected for development.
12 MAY 2015	A **Vaccines and Related Biological Products Advisory Committee** (VRBPAC) meeting was held. The licensing pathway for V920 and other Ebola vaccines in development was discussed, including "Traditional Approval", "Accelerated Approval" and "Animal Rule."
12 AUG 2015	Sponsorship of IND 16131 was transferred from NewLink Genetics to Merck Sharp & Dohme Corp.
25 SEPT 2015	An **Information Request** was provided to the Applicant for the V920-012 protocol, including a recommendation to include a lot-consistency success criterion for each pair-wise comparison to require 2-sided 95% CI on the GP-ELISA GMT ratio be greater than 0.67 and less than 1.5.
06 OCT 2015	A **Type C meeting** was held. Key discussions and responses included: the CMC information required for the BLA submission, plans for analytical bridging between the (b) (4) lots, the submission of the data from the Lot Consistency study (V920-012) to the BLA to increase the size of the clinical safety database, the planned submission of data from the V920-010 Guinea Ring Vaccination study to support efficacy of the vaccine, discussion of potential immunobridging strategies, and the approach to reproductive and developmental toxicity studies.

13 MAY 2016	CBER agreed to the **iPSP**, including the planned pediatric study, a partial waiver of the pediatric assessment for the pediatric population from 0 through 11 months of age, and a deferral for submission of the pediatric assessment for 12 months through 17 years of age.
26 MAY 2016	Request for **breakthrough therapy designation** was submitted and granted on June 29, 2016.
15 SEPT 2016	A **Type C Meeting** was held. Key discussions included: CBER's agreement that analytical data from emergency-use lots produced at a (b) (4) at the (b) (4) were comparable to analytical data from clinical lots produced by (b) (4) at the (b) (4) which provided support for the use of an analytical bridging approach for the final manufacturing facility in (b) (4). CBER also agreed that if the PPQ lots produced at the (b) (4) facility were analytically comparable to the (b) (4) lots used in the Phase 1-3 studies, then the (b) (4) DP lots used in the lot consistency study (V920-012) could be used to support the demonstrations of clinical consistency of V920. NOTE: The (b) (4) lots made at (b) (4) were designated for emergency use. All of the lots used in the clinical studies were made from the (b) (4) lots made at (b) (4).
24 JAN 2017	A **waiver** to allow clinical data to be submitted using the SDTM IG version 3.1.1 was granted.
30 JAN 2017	A **Type C Meeting** was held. Key discussions and responses included: CBER's agreement that the Traditional Approval pathway for licensure based on the non-IND Guinea Ring Vaccination Study efficacy data is a reasonable approach, providing the BLA application includes additional supportive safety and immunogenicity data, as well as data from non-human primate challenge studies and CBER's recommendation that the primary efficacy analysis be based on the endpoints that were pre-specified in the clinical study protocol and final statistical analysis plan (SAP): "all vaccinated in immediate versus all eligible and consented in delayed (consenting <10 days)," analyzed at the cluster level.
13 FEB 2017	CBER agreed that the PRNT assay was suitable for measuring neutralizing antibodies in human serum samples.
16 FEB 2017	CBER agreed that the IgG GP-ELISA assay was adequate for its intended use and testing of human samples could proceed. (This assay was validated under MF (b) (4), sponsored by The Surgeon General, Department of the Army).
22 JUN 2018	Draft rolling BLA submission **proposal** submitted. The Agency agreed with the submission of the "Nonclinical wave," the "CMC wave" and the "Clinical wave" in the rolling submission plan; however, they determined to start the review clock when DS PPQ data and comparability results have been submitted to the BLA.
11 OCT 2018	A **Pre-BLA Meeting** was held. Key discussions and responses included: CBER's agreement that the pre-clinical and clinical data packages were sufficient to support a substantive review of a BLA, CBER's request for English translated datasets for V920-010,

	agreement with the proposed content of the 4-month safety update report, plans regarding pre-licensing inspection of manufacturing facilities, and CBER's determination that a second VRBPAC would not be convened for this product. Agreement was reached on a rolling BLA submission, starting in October 2018 with nonclinical modules and ending in September 2019 with the DS PPQ results, and that data from DP PPQ Lots (b) (4) could be submitted postapproval.
11 NOV 2018	CBER agreed to start the review clock upon the submission of the interim report for (b) (4) PPQ lots.
15 JUL 2019	Interim report for (b) (4) PPQ lots was submitted and the review clock was started.

2.6 Other Relevant Background Information

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a clinical review without unreasonable difficulty; however, CBER identified several issues during the review.

A study data validation report identified multiple issues with the provided datasets, including data mapping to unexpected domains, missing variables, unexpected variable names, MedDRA coding errors, differences in adverse event reporting across datasets, unpopulated variables, and inconsistent values for laboratory reports or adverse events.

Reviewer comments: Some of the identified issues with the datasets were addressed via Information Requests to the sponsor to resolve discrepancies or were explained in the Analysis Data Reviewer's Guide for each study. The remaining issues with the datasets did not preclude the use of the datasets to perform clinical review activities.

Multiple clinical Information Requests (IRs) were sent and addressed in the following Applicant responses:

- Amendment 18: IR regarding the performance of confirmatory Ebola PCR testing for subjects with negative tests obtained by the Guinean health authorities.
- Amendment 31: IRs regarding data presented in the datasets and clinical study report (CSR) for V920-009, including CIOMs for SAEs, and V920-010.
- Amendment 37: IRs for data presented in the datasets and CSR for V920-012, including a request to provide narratives for SAEs reported during the extension study (Month 6 to Month 24).
- Amendment 42: IRs for data presented in the datasets and CSR for V920-010, including narratives for SAEs.
- Amendment 43: IRs for a tabular summary of the nominal dose, the actual dose, and the potency assay used for each study; safety analyses by sex and age for V920-009; clarification of safety data presented in the V920-011 CSR.
- Amendment 47: IRs regarding pregnancy data across the clinical development program.
- Amendment 48: IRs regarding pregnancy data in V920-011.

- Amendment 51: IRs regarding corrected pregnancy data from V920-011 as described in proposed labeling.
- Amendment 55: IRs regarding pregnancy data in V920-011.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Clinical studies V920-005, V920-006, V920-007, V920-008, and V920-010 were submitted according to 21 CFR 312.120, foreign clinical studies not conducted under a US IND.

- A description of research facilities; name of the IRB or IEC and statement that it met requirements as in 21 CFR 312.3 or was in compliance with ICH GCP; a summary of the IRB or IEC's decision to approve or modify the trial; and a description of how informed consent was obtained was provided for each study.
- A description of incentives provided to participants was provided or was available upon request for each study.
- Investigator's qualifications were provided for V920-005, V920-007, and V920-010. The curriculum vitae (CVs) for the Principal Investigators who participated in V920-006 and V920-008 were not made available at the time of finalization of the respective CSRs and are on file at the study centers.

All studies conducted under a US IND were conducted in accordance with GCP.

Reviewer's comment: The Applicant provided an in-depth accounting of protocol deviations which led or did not lead to subject elimination from analyses for all Phase 2/3 studies. Issues with consent processes were identified for V920-010 and V920-011 and were addressed with corrective action; a full review of these and other protocol deviations is included in the individual study reviews.

Reviewer's comment: All Phase 2/3 studies were assessed to determine the feasibility of a BIMO audit process. As the sole efficacy study, V920-010 was the primary candidate; however, the Applicant indicated that access to the source documents for this study was not possible due to binding agreements with the World Health Organization (WHO). WHO representatives were not available to facilitate access to study documents due to labor shortages related to the ongoing outbreak of Ebola in the DRC. Therefore, consensus was reached amongst the clinical review team, the Office of Vaccines Research and Review management, and the Office of Compliance and Biologics Quality leadership that the bioresearch monitoring (BIMO) audit process and report would be waived for this BLA submission due to operational issues.

In lieu of BIMO access to source documents for V920-010, the Applicant submitted an internal retrospective assessment report on the conduct of V920-010 as well as an independently-contracted audit of the study requested by the WHO and performed in August 2015 by (b) (4) .

Key findings from these reports included:

- One instance of GCP non-compliance regarding study data was identified by the study team, wherein fabricated data for study Day 3 were entered in the case report form (CRF) for 47 subjects. This was discovered prior to the next follow-up visit (Day 14) and corrective actions were taken to flag the invalid data, obtain the

Day 3 safety data, document and report noncompliance, and dismiss study personnel responsible for the fabrication.

- The independent audit did not identify any critical findings that would be likely to undermine the protection of persons or the reliability of data collected. Major observations addressed the readability and organization of study documents, the lack of clarity regarding study organization and operations, and inconsistencies between the database and source documents for SAEs. Descriptions of the corrective/protective action for each of the major observations was provided in a follow-up report.

Reviewer's comment: As a full BIMO inspection was not feasible for the BLA review, the available documentation for V920-010 was assessed and was considered sufficient to support the data integrity of the study.

3.3 Financial Disclosures

The Applicant provided a list of Investigators (n= 447) for the Phase 2/3 studies. A total of 444 investigators had certification of due diligence. Two sub-investigators (1 each from study V920-009 and V920-010) were unable to provide financial disclosure documentation. These sub-investigators were not responsible for individual enrollment of subjects or solely responsible for follow-up of individual subjects. One sub-investigator in study V920-012 reported an equity interest of >$50,000. This sub-investigator was not directly responsible for enrollment at this site, which was overseen by the primary investigator. This site enrolled 34 of the 1194 randomized/vaccinated subjects (2.8%) included in the study.

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

4.1 Chemistry, Manufacturing, and Controls

The vaccine dose designated for Phase 2 and 3 clinical trials (2×10^7 pfu) was assigned using a non-validated potency assay ((b) (4) method). Later during development, a modified potency assay, designed and validated at a new laboratory ((b) (4)), was used to establish the final release specifications for V920 Drug Product.

In the Phase 1 studies (V920-001 through V920-009), lot 003 05 13 was used, with a nominal dose of 1×10^8 pfu/mL used undiluted or diluted to achieve target doses for each study. The actual potency of this lot was 1.08×10^8 pfu/mL using the (b) (4) assay and 5.3×10^8 using the (b) (4) assay. In the Phase 2/3 studies (V920-009 [2 lots used in this study] through V920-012), lot 001 10 14 was used, with a nominal dose of 1×10^8 pfu/mL used undiluted or diluted to 2.0×10^7 pfu/mL. The actual potency of this lot at the diluted dose was 4.8×10^7 pfu/mL using the (b) (4) assay and 7.2×10^7 using the (b) (4) assay. Three additional lots (WL00060577, WL00060666, and WL00061283) were used for the lot-to-lot comparison groups in V920-012, all of which had a nominal dose of 2.0×10^7 pfu/mL and actual potencies of 6.6×10^7, 6.6×10^7, and 5.4×10^7 pfu/mL using the (b) (4) assay, respectively. The (b) (4) assay was not performed for these lots.

The CMC Reviewer recommended approval of the product, concluding that that:

- The sponsor showed data ensuring that master cell banks, working cell banks, virus master seed used in the production of the vaccine are free of

extraneous agents. The sponsor presented information ensuring safety from BSE/TSE concerns. The final vaccine formulation does not contain any new or known hazardous excipients and is therefore considered devoid of any toxicity. The sponsor presented results showing that the consistent elimination of all impurities throughout the drug substance manufacturing process.

- The vaccine manufacturing process is robust, and the virus titers achieved are consistent. The sponsor performed in-process and release testing of the vaccine and its intermediates at different stages of manufacturing intended to ensure that the product meets specifications and is consistent.
- Acceptance specification for the potency of the vaccine is (b) (4) . The minimum release specification has been calculated as (b) (4) based on the expiry specification of 7.2×10^7 pfu/mL at the end of expiry period of 36 months. Data from the clinical studies have shown that the vaccine is immunogenic and protective at a dose of 7.2×10^7 pfu/mL, and therefore, a minimum release potency specification of 7.2×10^7 pfu/mL is acceptable.

Reviewer's comment: Please see the CBER CMC review for additional details. Although the potencies of the lots were reassigned using values from the (b) (4) *assays and these potencies were adopted for release specifications, this clinical review uses the potency designations referred to in the CSRs and datasets for each study (i.e., nominal dose of 2 x 10^7 pfu/dose for the Phase 2/3 studies).*

4.2 Assay Validation

Evaluation of V920 for licensure was based on the results of analyses of clinical endpoints assessed using the (b) (4) Ebolavirus RT-PCR Kit (b) (4).

Immunogenicity data was collected using validated assays in V920-009, V920-011, and V920-012 including:

- Zaire Ebola Virus Anti-Glycoprotein Immunoglobulin G Human ELISA (GP-ELISA): To measure and quantify total immunoglobulin G (IgG) binding antibodies against V920, an indirect ELISA was developed which utilizes a purified recombinant glycoprotein (rGP) as the coating antigen and an enzyme-conjugated anti-human IgG secondary antibody as the reporter or signal system. Titers were reported as GP-ELISA units/mL.
- V920 Plaque Reduction Neutralization Test (PRNT): To measure and quantify neutralizing antibodies against V920, a PRNT assay was developed that neutralizes the recombinant vesicular stomatitis virus with envelope glycoprotein replaced by Zaire Ebola virus (Kikwit Strain) glycoprotein (V920) vaccine strain. Determination of the neutralizing titer was based upon the percent reduction in viral plaques in the presence of serum compared to that of the virus control without serum.

Across the Phase 2/3 studies if a measurement was below the LLOQ for either assay, ½ LLOQ was used for the calculation of GMT, fold-rise, and seroconversion.

Reviewer's comment: The CBER assay reviewer confirmed that the immunologic assays used in the development program have adequate performance for use in clinical studies V920-009, V920-011, and V920-012 and that the determination of EVD cases in V920-010 was sufficiently reliable to support the use of the results of the study as substantial evidence of effectiveness. Please refer to the CBER Non-clinical statistical review for additional details.

The RT-PCR assays used to demonstrate the vaccine virus viremia and shedding in vaccinees across the Phase 1/2 clinical studies were conducted by different laboratories using the assays, which were not standardized across different clinical sites where the Phase 1/2 clinical studies were conducted. The qualification parameters for the RT-PCR assays, such as a limit of detection (LOD) and a lower limit of quantification (LLOQ), including the LODs measured for different tested clinical matrices (e.g., blood, urine, synovial fluid) were not identical across the clinical studies.

Reviewer's comment: Due to the variability in RT-PCR assays for vaccine viremia and shedding across the studies, variations in the percentages of vaccinees with viremia and shedding at different clinical sites cannot be precisely evaluated. Please refer to the CBER CMC review for additional details regarding assay validation.

4.3 Nonclinical Pharmacology/Toxicology

Nonclinical toxicology

The Toxicology reviewer reviewed three dedicated toxicology studies, including a repeat-dose toxicity study in mice, repeat-dose toxicity study in cynomolgus macaques, and a developmental toxicity in rats. An exploratory neurovirulence study in cynomolgus Macaques, a preliminary viremia and immunogenicity study in rats and an *in vivo* biodistribution and persistence in cynomolgus macaques were also submitted to the BLA but were not reviewed as they were considered preliminary or exploratory. Key highlights of the Toxicology review include:

- In the repeated toxicity study in mice, three groups of animals (30/sex/group) received intramuscular (IM) injections of saline control, 0.2 mL of 2 x 10^6 pfu V920, or 0.2 mL of 2 x 10^7 pfu V920 on Days 0 and 14. Blood specimens were collected on Days 16 and 44 for clinical pathology, immunogenicity, and viremia. Urine specimens were collected on Days 0, 2 and 6 for viruria analysis. On Day 16, half of the mice were humanely terminated for post-mortem evaluations. On Day 44, the remaining half of the mice were humanely terminated for post-mortem evaluation. There were no biologically significant V920-related effects on clinical observations, mortality, body weights, body temperature, clinical chemistry and hematology. Higher spleen weights and enlargement of iliac lymph nodes were reported in both groups. Microscopic findings noted at Day 16 were observed at reduced incidences and/or severity at the end of recovery period on Day 44. These gross observations along with their corresponding microscopic findings of lymphoid hyperplasia were an expected immunogenic response to the vaccine administration. Robust antibody titers on Days 16 and 44 were indicative of an active delivery of the test articles in the treated animals.
- In the repeated toxicity study in cynomolgus macaques, total of 14 males and 14 females received IM injections of saline control (2/sex/group), 1 mL of 3 x 10^6 pfu V920 (6/sex/group), or 1 mL of 1 x 10^8 pfu V920 (6/sex/group) on Days 0 and 14. Samples were collected for clinical pathology, immunogenicity evaluation, and viremia analysis. Urine specimens were collected for viruria

analysis. On Day 16, all placebo recipients and four animals/sex from V920 groups were humanely terminated for post-mortem evaluations. On Day 44, the remaining eight animals in the V920 groups were humanely terminated for postmortem evaluations. There were no biologically significant V920-related effects on clinical observations, mortality, body weights, body temperature, coagulation, hematology, gross pathology and organ weights. Elevated fibrinogen along with less clear significant elevation of C-reactive protein was reported in the High Dose group. Microscopic findings were limited to the injection sites (inflammation) and inguinal lymph node (lymphoid hyperplasia). These findings were typical local and/or immunogenic responses to vaccine administration. Robust antibody titers on Days 16 and 44 were indicative of an active delivery of the test articles in the treated animals.

- In the reproductive toxicity study, a total of 132 (b) (4) female rats were randomized 1:1:1 to Groups 1, 2, and 3 (n= 44 each). Within each group, the 44 rats were assigned to two subgroups (Subgroups A and B), approximately equally, on the basis of confirmed mating dates. F0 generation female rats in the control and V920 immunogenicity groups (Groups 1 and 2, respectively) received IM phosphate buffered saline (PBS) or 5.28×10^7 pfu (0.22 mL) V920 on Day 1 of study (28 days prior to cohabitation), Day 22 of study (7 days prior to cohabitation), Day 6 of gestation, and Day 7 of lactation. Female rats in the V920 viremia group (Group 3) received a single vaccination administration on Day 6 of gestation. There were no vaccine-related mortalities or clinical or necropsy observations in the dams or in the pups. It had no impact on mating and fertility parameters, ovarian and uterine examination, or natural delivery or litter observation parameters in the dams. There were no fetal external, soft tissue, or skeletal abnormalities attributed to vaccine administration. Postnatal development as measured by acoustic (auditory) startle, air righting, and pupil constriction, and functional observational battery parameters in the pups were unaffected.

Reviewer comments: The Toxicology reviewer did not identify any major safety concerns. The Toxicology reviewer indicated that the BLA has adequate nonclinical toxicology data in support licensure of the vaccine. For additional details, please see the full Toxicology review.

Nonclinical pharmacology

The CMC reviewer evaluated the primary pharmacodynamic properties of V920 in multiple non-Good Laboratory Practice (non-GLP) immunogenicity and efficacy studies rodents and in non-human primates (NHP). Key studies in NHP studies are as follows:

- Evaluation of the prophylactic efficacy of V920 and related candidate vaccines in NHP (published studies)
  - In published studies in NHP using oral, (b) (4) or IM doses of 1×10^7 pfu or higher V920, protection was 100% against a 1000 pfu IM challenge with ZEBOV virus at Days 7, 14, 21, and 28. In a study assessing challenge at Day 3 after vaccination, two of three NHP had illness and two of three NHP survived.
- Evaluation of the durability of protective immunity (published studies)
  - A published NHP study demonstrated that immunization of cynomolgus macaques with a rVSVΔG vaccine expressing the Marburg virus (MARV) GP induced long-lasting IgG titers and protected against IM MARV challenge 14 months after vaccination.

- Evaluation of the immunogenicity and efficacy in NHP in studies conducted at the United States Army Medical Research Institute for Infectious Diseases (USAMRIID), Ft. Detrick, Maryland, USA:
    - In three studies assessing a single IM dose of V920 at doses between 3 x 10^2 and 1 x 10^8 pfu followed by an IM challenge ZEBOV dose of 1000 pfu, immunogenicity was demonstrated in all animals and survival was between 96 and 100% following challenge at Day 42 post-vaccination, 33% following a challenge at Month 3 post-vaccination, and 43% following a challenge at Month 12 post-vaccination.
    - (b) (4)

In the biodistribution study, persistence of vaccine viral RNA was observed primarily in lymphoid tissues by qRT-PCR throughout the duration of the study (112 days). A subsequent plaque assay detected replication-competent virus limited to day 1 post-vaccination, with no evidence of viral replication at any other time point measured (days 56, 84, and 112). Viral RNA after Day 7 was generally confined to tissues lacking potential for shedding in excretions or secretions and showed no evidence of distribution to the brain or spinal cord at any time point.

In the exploratory neurovirulence study, two of three animals administered wt-rVSV showed severe neurological symptoms, whereas animals receiving vehicle control, V920, or rVSVΔG-MARV-GP did not develop these symptoms. Significant neuropathologic changes were observed in the wt-rVSV inoculated animals. However, no significant histomorphological lesions were observed in the neural tissues of any animals from rVSVΔG-ZEBOV-GP-treated monkeys.

Reviewer comments: Per the CMC reviewer, these data suggest that the rVSVΔG-ZEBOV-GP vaccine virus lacks the neurovirulence properties associated with wild-type VSV. No additional neurovirulence studies were performed by the Applicant for this vaccine product. For additional details on NHP studies of biodistribution and neurovirulence, please see the full CMC review.

4.4 Clinical Pharmacology

Pharmacodynamic data, comprised of immune response to the vaccine, can be found in the reviews of the clinical studies that included immunogenicity assessments.

4.4.1 Mechanism of Action

V920 induces an immune response to the EBOV glycoprotein (GP), a protein expressed on the virion surface. The specific immune response that confers protection against EVD is unknown.

4.4.2 Human Pharmacodynamics (PD)

Pharmacodynamic data, comprised of immune response to the vaccine, can be found in the review of the clinical studies.

4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses cited by the Applicant were supported by the submitted data. Clinical efficacy of V920 Ebola vaccine was evaluated only in V920-010 (Guinea Ring Vaccination Study). As there were no EVD cases observed in the immediate vaccination arm after Day 10, the point estimate of VE is 100% regardless of the statistical model. However, the lower bound of the 95% CI of VE is 15.5% based on the estimation of efficacy at the ring level, while it is 63.5% based on the applicant's estimation of efficacy at the individual subject level. The most conservative analysis is the one at the ring level.

Reviewer's comment: See the Statistical review for additional details.

4.6 Pharmacovigilance

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

CBER is including a PREA PMR as part of approval.

Reviewer's comment: The Applicant submitted a revised RMP/PVP (Version 2.0, dated August 23, 2019) to remove "safety and reduced efficacy in immunocompromised hosts" as a potential risk. Although CBER recommended that the PVP include both "arthritis" and "safety and reduced efficacy in immunocompromised hosts" as potential risks, the Applicant indicated that no additional pharmacovigilance activities are planned to further characterize these potential risks. CBER accepted the Applicant's decision to not include "arthritis" and "safety and reduced efficacy in immunocompromised hosts" in the PVP, as data regarding these potential risks will be available for analysis through routine pharmacovigilance. The proposed pharmacovigilance plan for ERVEBO included in the RMP, version 2.0, dated August 23, 2019, is adequate for the labeled indication.

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

5.1 Review Strategy

Effectiveness

V920-010 was the sole efficacy study conducted and the evaluation of efficacy is limited to the data generated from this study.

Immunogenicity data are available from three Phase 2/3 studies, V920-009, V920-011, and V920-012. An integrated analysis of this immunogenicity data is planned but was not provided in the BLA. Therefore, the immunogenicity data are reviewed separately for each study in Section 6 of this review. Immunogenicity data for the Phase 1 studies are provided in Appendix 1; however, the specimens from these studies were not evaluated using validated assays.

Safety

The studies submitted to support this BLA were conducted by multiple sponsors, resulting in various methods of safety data collection. Therefore, the integration of safety data was limited to an analysis of serious adverse events (SAEs) reported from the blinded studies, including all blinded Phase 1 studies and the blinded Phase 2/3 studies (V920-009 and V920-012). This approach excludes the largest studies in the clinical database, V920-011 and V920-010, from the integrated analysis. In addition to the integrated analysis of SAEs, the safety data are reviewed separately for each study in Section 6 of this review. A summary of safety findings categorized by blinded studies and open label studies is provided in Section 8, along with the integrated safety analysis. Key safety findings from Phase 1 studies are provided in Appendix 1.

CBER utilized safety review tools to evaluate safety data by MedDRA hierarchies (using JMP) and MedDRA hierarchies and SMQs (utilizing a safety analytic software tool developed by FDA).

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

Presented below are the amendments, modules and content that were assigned to and reviewed by the clinical reviewer.

- 125690/0 (received 24-OCT-2018): Sections 1.6 (Meetings), 1.7 (Fast Track), 1.9 (Pediatric Administrative Information), 1.4 (Labeling), 1.16 (Risk Management Plan), 1.18 (Proprietary Names)
- 125690/1 (received 13-DEC-2018): Sections 1.3 (Debarment Certification and Financial Certification and Disclosure), 1.6 (Meetings), 1.11 (Clinical Information Amendment), 1.13 (Annual Report), 1.14 (Labeling), 2.5 (Clinical Overview), 2.7 (Clinical Summary), 5.2 (Tabular Listing of all Clinical Studies), 5.3.5 (Reports of Efficacy and Safety Studies)
- 125690/2 (received 15-JAN-2019): Section 1.11.3 (Efficacy Information Amendment)
- 125690/8 (received 22-FEB-2019): Section 1.11.3 (Clinical Information Amendment: Datasets supporting V920-010), 5.3.5 (Reports of Efficacy and Safety Studies: Updated CSRs for V920-009 and V920-012)
- 125690/9 (received 28-FEB-2019): Section 1.11.3 (Clinical Information Amendment: Response to CBER IRs of 22-FEB-2019)
- 125690/11 (received 18-MAR-2019), 125690/13 (received 29-MAR-2019), 125690/18 (received 22-MAY-2019): Section 1.11.3 (Clinical Information Amendment: Responses to CBER IRs of 22-FEB-2019, Assessment Report for V920-010, and Responses to CBER IRs of 27-MAR-2019, respectively)

- 125690/23 (received 18-JUL-2019): Section 2.7 (Clinical Summary: 4-month Safety Update Report) and 5.3.5 (Reports of Efficacy and Safety Studies: narratives for 4-month Safety Update report)
- 125690/31 (received 5-SEP-2019): Section 1.11.3 (Clinical Information Amendment: Responses to CBER IRs of 15-AUG-2019) and 5.3.5 (Reports of Efficacy and Safety Studies: narratives for V920-009)
- 125690/32 (received 5-SEP-2019): Section 1.16 (Risk Management Plan)
- 125690/33 (received 9-SEP-2019): Section 1.9 (Pediatric Administrative Information)
- 125690/37 (received 01-OCT-2019): Section 1.11.3 (Clinical Information Amendment: Responses to CBER IRs of 17-SEP-2019) and 5.3.5 (Reports of Efficacy and Safety Studies: subject data listings for V920-012)
- 125690/41 (received 15-OCT-2019): Section 1.11.3 (Clinical Information Amendment: Package insert update) and Section 1.14 (Labeling)
- 125690/42 (received 15-OCT-2019): Section 1.11.3 (Clinical Information Amendment: Responses to CBER IRs of 17-SEP-2019) and 5.3.5 (Reports of Efficacy and Safety Studies: narratives and case report forms for V920-010)
- 125690/43 (received 24-OCT-2019) and 125690/47 (received 06-NOV-2019): Section 1.11.3 (Clinical Information Amendment: Responses to CBER IRs of 30-SEP-2019 and Responses to CBER IRs of 22-OCT-2019)
- 125690/47 (received 06-NOV-2019): Section 1.11.3 (Clinical Information Amendment: Responses to CBER IRs of 22-OCT-2019)
- 125690/48 (received 06-NOV-2019): Section 1.11.3 (Clinical Information Amendment: Responses to CBER IRs of 21-OCT-2019)
- 125690/51 (received 02-DEC-2019): Section 1.11.3 (Clinical Information Amendment: Supporting data for USPI and responses to IR of 21-NOV-2019)
- 125690/55 (received 11-DEC-2019): Section 1.11.3 (Clinical Information Amendment: Pregnancy data for V920-011)
- 125690/58 (received 17-DEC-2019): Section 1.11.3 (Clinical Information Amendment: Response to IR for V920-010)

5.3 Table of Studies/Clinical Trials

The following table summarizes the Phase 1 studies. Study endpoints for all Phase 1/1b studies were descriptive safety and immunogenicity.

Table 4 Phase 1 studies

Study ID	Phase	IND study	Country	Study design	V920 dosing regimen and exposure (n)	Study population
V920-001	1	Yes	United States	Randomized, single center, double-blind, placebo-controlled, dose-escalation	3×10^6 pfu (n=10), 2×10^7 pfu (n=10), 1×10^8 pfu (n=10), placebo (n=9)	Healthy eligible subjects (18- 50 YOA)
V920-002	1	Yes	United States	Randomized, single center, double-blind, placebo-controlled, dose-escalation (2 dose series)	3×10^6 pfu (n=10), 2×10^7 pfu (n=10), 1×10^8 pfu (n=10), placebo (n=9) on Days 0 and 28	Healthy eligible subjects (18-65 YOA)

Study ID	Phase	IND study	Country	Study design	V920 dosing regimen and exposure (n)	Study population
V920-003	1	Yes	Canada	Randomized, single center, double-blind, placebo-controlled, dose-ranging	1×10^5 pfu (n=10), 5×10^5 pfu (n=10), 3×10^6 pfu (n=10), placebo (n=10)	Healthy eligible subjects (18-65 YOA)
V920-004	1b	Yes	United States	Randomized, multicenter, double-blind, placebo-controlled, dose-response	3×10^3 pfu (n=64), 3×10^4 pfu (n=64), 3×10^5 pfu (n=64), 3×10^6 pfu (n=84), 9×10^6 pfu (n=47), 2×10^7pfu (n=47), 1×10^8 pfu (n=48), placebo (n=94)	Healthy eligible subjects (18-60 YOA)
V920-005	1	No	Switzerland	Randomized, single center, double-blind, placebo-controlled, dose-finding	3×10^5 pfu (n=51), 1×10^7 pfu (n=35), 5×10^7 pfu (n=16), placebo (n=13)	Healthy eligible subjects (18-65 YOA)
V920-006	1	No	Germany	Open label, single center, dose escalation	3×10^5 pfu (n=10), 3×10^6 pfu (n=10), 2×10^7 pfu (n=10)	Healthy eligible subjects (18-55 YOA)
V920-007	1	No	Gabon	Open label, single center, Dose escalation	3×10^3 pfu (n=20), 3×10^4 pfu (n=19), 3×10^5 pfu (n=20), 3×10^6 pfu (n=39), 2×10^7 pfu (n=16), 2×10^7 pfu (n=20; 6-12 YOA) (n=20; 13-17 YOA)	Healthy eligible subjects (6-50 YOA)
V920-008	1	No	Kenya	Open label, single center, Dose escalation	3×10^6 pfu (n=20), 2×10^7 pfu (n=20)	Healthy eligible adult health workers (18-55 YOA)

YOA= years of age

Reviewer's comment: The Phase 1 blinded studies contributed safety and supportive immunogenicity data to the clinical review. Summary reviews of V920-001 through V920-008 are located in Appendix 1.

Table 5 Phase 2/3 studies

	V920-009	V920-010	V920-011	V920-012
Phase	2	3	2/3	3
IND study	Yes	No	Yes	Yes
Country	Liberia	Guinea	Sierra Leone	United States, Canada, Spain
Study design	Randomized, single center, double-blind, placebo-controlled	Open-label, cluster randomized, controlled, ring vaccination	Randomized, multicenter, open-label	Randomized, multicenter, double-blind, placebo-controlled

	V920-009	V920-010	V920-011	V920-012
V920 dosing regimen and exposure (n)	2×10^7 pfu (n=500), placebo (n=500)	2×10^7 pfu Randomized Subjects • Immediate Vaccination: (n=2119) • Delayed Vaccination: (n=2041) Non-randomized Subjects • Immediate Vaccination: (n=1677 including n=194 subjects 6 to <18 YOA)	2×10^7 pfu • Immediate Vaccination (n= 4165) • Deferred Vaccination: (n= 12*) • Deferred Vaccination Crossover (n= 3821)	2×10^7 pfu, (n=266, 265, and 266 for each lot) 1×10^8 pfu, (n=264) placebo (n=133)
Study population	Eligible subjects (≥18 YOA)	Randomized Subjects living in the defined vaccination ring (>18 YOA) Non-randomized Subjects who are contacts or contacts of contacts of an EVD case (≥ 6 YOA)	Subjects at high risk of exposure to EVD (≥18 YOA)	Healthy eligible subjects (18 to 65 YOA)
Study endpoints	Safety and immunogenicity	Efficacy and safety	Safety and immunogenicity	Safety and immunogenicity (lot consistency)
Location in review (Section)	6.2	6.1	6.4	6.3

YOA= years of age; EVD= Ebolavirus disease
*vaccinated in error

5.4 Consultations

Pediatric Review Committee (PeRC)

This submission is subject to the Pediatric Research Equity Act (PREA). FDA's Pediatric Review Committee (PeRC) and CBER agreed with the Applicant's request for a waiver of pediatric assessments for children from birth through 11 months of age as the studies are impossible or highly impracticable (e.g. the number of pediatric patients is so small or is geographically dispersed) (section 505B(a)(5)(B)(i)). The PeRC and CBER agreed with the Applicant's plan for a deferral of the pediatric assessment for children 12 months through 17 years of age as the drug or biological product is ready for approval for use in adults before pediatric studies are complete (section 505B(a)(4)(A)(i)(I)).

5.4.1 Advisory Committee Meeting

On May 12, 2015, the Vaccines and Related Biological Products Committee (VRBPAC) was convened to discuss pathways to licensure for Ebola vaccines. Two discussion items were included in the agenda: 1) the use of immune markers derived from human and non-human primate studies to demonstrate the effectiveness of Ebola vaccines; and 2) approaches to post-licensure studies to verify the clinical benefit of development and licensure pathways for Ebola Vaccines in the event an Ebola vaccine is approved using the Accelerated Approval pathway or the "Animal Rule." In the discussions, there was general agreement that there was potential for the use of immune markers to support licensure. The discussion of appropriate post-marketing study designs to follow licensure

via the Accelerated Approval pathway or Animal Rule included long-term prospective studies and short-term test-negative studies.

Reviewer comment: The issues addressed in the VRBPAC meeting did not apply to this product as the licensure pathway for this product was based on a clinical endpoint field-efficacy study, and not via Accelerated Approval or Animal Rule.

5.5 Literature Reviewed

1. Bebell, Lisa M., Titilope Oduyebo, and Laura E. Riley. "Ebola virus disease and pregnancy: A review of the current knowledge of Ebola virus pathogenesis, maternal, and neonatal outcomes." Birth defects research 109.5 (2017): 353-362.
2. Clark, Danielle V., et al. "Long-term sequelae after Ebola virus disease in Bundibugyo, Uganda: a retrospective cohort study." The Lancet Infectious Diseases 15.8 (2015): 905-912.
3. Dokubo, Emily Kainne, et al. "Persistence of Ebola virus after the end of widespread transmission in Liberia: an outbreak report." The Lancet Infectious Diseases 18.9 (2018): 1015-1024.
4. Fallah, Mosoka P., et al. "Pregnancy outcomes in Liberian women who conceived after recovery from Ebola virus disease." The Lancet Global Health 4.10 (2016): e678-e679.
5. Kennedy SB, Bolay F, Kieh M, Grandits G, Badio M, Ballou R, et al. Phase 2 Placebo-Controlled Trial of Two Vaccines to Prevent Ebola in Liberia. N Engl J Med. 2017 Oct 12;377(15):1438-1447.
6. Khurana, Surender, et al. "Human antibody repertoire after VSV-Ebola vaccination identifies novel targets and virus-neutralizing IgM antibodies." Nature medicine 22.12 (2016): 1439.
7. Kugelman, Jeffrey R., et al. "Monitoring of Ebola virus Makona evolution through establishment of advanced genomic capability in Liberia." Emerging infectious diseases 21.7 (2015): 1135
8. Malvy, Denis, et al. "Ebola virus disease." The Lancet (2019).
9. Qureshi, Adnan I., et al. "Study of Ebola virus disease survivors in Guinea." Clinical Infectious Diseases 61.7 (2015): 1035-1042.
10. Henao-Restrepo, Ana Maria, et al. "Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!)." The Lancet 389.10068 (2017): 505-518.
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13. Tiffany, Amanda, et al. "Ebola virus disease complications as experienced by survivors in Sierra Leone." Clinical Infectious Diseases 62.11 (2016): 1360-1366.
14. CDC. 2014-2016 Ebola Outbreak in West Africa. Retrieved from https://www.cdc.gov/vhf/ebola/history/2014-2016-outbreak/index.html
15. WHO. Ebola virus disease. Retrieved from https://www.who.int/health-topics/ebola/#tab=tab_1

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17. WHO. Ebola outbreak 2014-2016. Retrieved from https://www.who.int/csr/disease/ebola/en/
18. WHO. Ebola Virus Disease Democratic Republic of Congo: External Situation Report 71 / 2019. Retrieved from https://www.who.int/publications-detail/ebola-virus-disease-democratic-republic-of-congo-external-situation-report-71-2019
19. WHO. Preliminary results on the efficacy of rVSV-ZEBOV-GP Ebola vaccine using the ring vaccination strategy in the control of an Ebola outbreak in the Democratic Republic of the Congo: an example of integration of research into epidemic response. Retrieved from https://www.who.int/csr/resources/publications/ebola/ebola-ring-vaccination-results-12-april-2019.pdf

6.1 Trial #1

V920-010: A Randomized Trial to Evaluate Ebola Vaccine Efficacy and Safety in Guinea, West Africa
Date of first enrollment: March 23, 2015
Date of last subject visit: January 20, 2016
Database lock: April 20, 2016
Sponsor name: World Health Organization (WHO)

6.1.1 Objectives

The primary objective of V920-010 was to assess vaccine efficacy against laboratory-confirmed Ebola virus disease (EVD) by performing a clinical trial comparing immediate versus delayed ring vaccination.
The secondary objectives of the study were as follows:

- To assess overall vaccine effectiveness (cumulative incidence) in preventing laboratory-confirmed EVD at the level of the ring after 84 days of follow-up.
- To assess vaccine efficacy against death from laboratory-confirmed EVD.
- To assess vaccine efficacy against probable and suspected EVD.
- To evaluate vaccine safety by assessing serious adverse events (SAEs) over 84 days.
- Estimation of transmission parameters.

Reviewer's comment: Due to the low numbers of EVD cases that did not have testing available, the assessment of vaccine efficacy against probable and suspected EVD was not performed. The analysis of the estimation of transmission parameters was not available at the time of submission of the BLA. Further details are provided below.

6.1.2 Design Overview

V920-010 is a field-based, Phase 3, open-label, cluster-randomized, controlled ring vaccination trial, designed to evaluate the efficacy, effectiveness, and safety of a dose of V920 in the prevention of EVD during the 2014-2016 outbreak in Guinea. Initial treatment clusters included adult subjects randomized to receive either immediate or delayed (21 days after randomization) vaccination with V920. Due to an interim analysis demonstrating 100% vaccine efficacy and the waning Ebola outbreak in Guinea, the Data Safety Monitoring Board (DSMB) recommended discontinuation of randomization

procedures, immediate vaccination for all identified rings, and inclusion of children 6-18 years of age (protocol amendment 4 dated July 8, 2015). Protocol amendment 5 (dated September 14, 2015) expanded vaccination to areas of Sierra Leone adjoining the border of Guinea. The total duration of the study period from first enrolled subject to Day 84 visit of the last subject followed was 303 days (~10 months).

Index cases of EVD were identified by the Guinean national surveillance system. A separate WHO study team composed of local social mobilization experts visited the area of residence of each case to obtain community consent for the trial team to enumerate a new cluster and provide ongoing community engagement. The ring definition team defined the cluster population by creating a list of all contacts and contacts of contacts (CCC), relative to the index case, regardless of eligibility for vaccination, including absent contacts and contacts of contacts. From the complete cluster list, preliminary inclusion and exclusion criteria were applied (e.g. age) to generate a list of all potential trial participants (eligible CCCs) to be approached for consent. Once the cluster list was finalized and closed, eligible CCCs were cluster-randomized to immediate or delayed vaccination (21 days later). Allocation of a cluster was done once the enumeration of the cluster (i.e., the list of CCCs) was done. A separate consent team obtained written informed consent from all eligible CCCs. Eligible CCCs cluster-randomized to immediate vaccination had only one opportunity to give their informed consent (Day 0), while eligible CCCs assigned to the delayed clusters had an opportunity to consent on Day 0 and/or Day 21. Subjects were informed of the cluster allocation at the end of the informed consent process.

Reviewer's comment: The choice of a cluster-randomized controlled study design was informed by multiple factors, including the history of the surveillance-containment strategy that led to smallpox eradication, conditions in the field in Guinea during the outbreak, and recommendations by public health organizations. Potential sources of bias introduced by this study design include:

- *Imbalances in the clusters, such as risk of EVD (e.g. number of EVD exposures and type of exposure), size, and consent behaviors.*
- *Ascertainment bias: detection of EVD cases may have been affected by the open-label study design.*
- *Performance bias: study personnel interacted with subjects in the immediate vaccination clusters more frequently than the delayed vaccination clusters during the primary analysis period (due to data collection procedures for AEs), which may have resulted in differential exposure to Ebola prevention interventions*

However, other study designs, which may have resulted in a reduction in bias, were not deemed feasible due to the need for larger populations and longer study durations. Throughout the following clinical review of this study, features of the study procedures and analysis approach that attempt to address these and other potential sources of bias are discussed.

6.1.3 Population

Inclusion Criteria

A cluster was categorized as urban (cities and suburbs) or rural (towns, hamlets or other non-urbanized areas) and was comprised of all CCCs of an index case of EVD as defined below. A new cluster was defined if at least 60% of the CCCs were not enumerated in a previous cluster. Individuals already enrolled in a cluster were excluded

from participation in a new cluster (including those who had not yet been vaccinated and those who refused vaccination).

Contacts were identified as anyone who met any of the following criteria:

- all persons who lived with the index case since the appearance of the disease;
- all persons who visited the index case at home or in a health center since the appearance of the disease;
- all places and persons visited by the patient since the appearance of the disease (for example, the traditional healer, church, loved ones);
- all health centers visited by the patient since the appearance of the disease, all healthcare workers in contact with the patient (living or dead) without appropriate protective measures;
- all persons in contact with the body of the patient from the time of death until funeral ceremonies; and
- anyone identified during home visits by the contact research and tracking teams who may have been exposed to the patient (living or dead) but who were not identified and listed previously as contacts during the stages listed above.

High-risk contacts included persons who:

- touched the patient's body fluids (i.e., blood, vomit, saliva, urine, fecal matter);
- were in direct physical contact with the patient's body (living or dead);
- touched or cleaned the linens, clothes, or kitchenware of the patient or cleaned the linen or the of the patient; or
- slept or ate in the same household as the patient.

Contacts of contacts included:

- neighbors or extended family members living in the same geographical area as the local contacts of the index case, typically within a delineated residential area such as a residential plot (the boundaries may be a wall, fencing, or where the area is bounded by open space between residences such as a road, path, field or forest) or
- residents of a dwelling in which a high-risk contact lives (see definition above) who does not live in the same community as the case.

Initially, only individuals who were 18 years of age and older were eligible. After the results of an interim efficacy analysis were available, the protocol was amended allow enrollment of subjects down to 6 years of age.

Reviewer's comment: *The protocol was modified in response to the DSMB recommendation to stop randomization and vaccinate all participants immediately. The primary efficacy analysis only included adult data collected prior to the study being opened to enrollment of pediatric subjects.*

<u>Exclusion Criteria</u>

- History of EVD (self-reported or laboratory confirmed).
- Pregnancy (self-reported) or breast-feeding. Women were offered, but not required, to take a pregnancy test.
- History of having received other experimental treatments in the previous 28 days.
- Serious illness that made the person bed-bound or required hospitalization at the time of the vaccination.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Clusters were randomly assigned in a 1:1 ratio to receive the investigational product at either Day 0 (immediate clusters) or Day 21 (delayed clusters) after individuals from the defined cluster were consented.

V920 was formulated with 2.5 g/L recombinant human serum albumin (rHSA) and 10mM Tris (b) (4), and the trial vaccine was provided in 1 mL vials that had a nominal titer of $1x10^8$ pfu/mL of vaccine virus. On the day of vaccination, vaccine was thawed at ambient temperature and stored at (2-8°C) until used to prepare dilution. Three 1-mL vials of vaccine were diluted with one 10-mL vial of diluent (0.9% sodium chloride) to prepare dilution for up to 13 subjects. A single lot was used (Lot Number 011 10 14).

Reviewer's comment: Please see Section 4.1 (Chemistry, manufacturing, and controls) for additional details on vaccine potency for V920-010.

6.1.5 Directions for Use

A single 1 mL dose of the vaccine was administered intramuscularly in the deltoid muscle, preferably in the non-dominant arm.

6.1.6 Sites and Centers

The trial was based in Basse-Guinée, a coastal area of Guinea, West Africa, and comprised the capital Conakry and eight surrounding prefectures in Guinea. In addition, following the interim analysis and implementation of Version 5 of the protocol, two prefectures (Kambia and Bombali) in Sierra Leone were included.

The following table describes the distribution of randomized rings by prefecture.

Table 6 Distribution of rings by prefecture

Prefecture name	Number of immediate rings	Number of delayed rings
Boke	3	3
Bombali	0	0
Conakry	10	7
Coyah	0	0
Dubreka	6	4
Forecariah	31	30
Fria	1	2
Kambia	0	0
Kindia	0	1

Source: Original BLA 1251690/2; Clinical Study Report V920-010, p.63

Reviewer's comment: As there might be geographic differences with regard to risk of EVD, it is reassuring that randomization resulted in a relatively similar number of immediate and delayed rings for each prefecture.

In the non-randomized portion of the study, rings were from the following prefectures: Bombali (n= 1), Conakry (n= 10), Coyah (n= 2), Forecariah (n= 5), and Kambia (n =1).

6.1.7 Surveillance/Monitoring

Safety and efficacy data were legibly recorded in black ink using standardized paper Case Report Forms (CRFs). Data were also collected from source documents designated in the protocol, including the WHO Ebola case investigation form, Ebola laboratory results, Ebola surveillance contact tracing form, Ebola contact tracing line list, and contact follow up form.

An independent 6-member data safety monitoring board (DSMB) was set up prior to the start of the trial. The DSMB assessed safety and efficacy throughout the trial period, including a real-time blinded review on a monthly basis based on the monthly summary updated reports, reviews of efficacy data per group, and reviews of all reported SAEs, and made recommendations as appropriate.

EVD surveillance
EVD surveillance was actively conducted by the Guinean Ministry of Health (MOH) and the WHO surveillance center. Active case finding of unreported EVD cases included daily follow up of contacts of cases for 21 days (contact tracing) by a MOH/WHO surveillance team, scheduled follow-up visits for adverse event (AE) and SAE monitoring in the communities, and reporting by community ring representatives.

All cases of EVD identified before the randomization of the index case were recorded and geographically located together with their identified contacts. New cases of EVD admitted to the Ebola treatment center (ETC) were routinely cross-matched to the lists of eligible populations in the vaccinated rings (both immediate and delayed vaccination rings). Confirmed Ebola cases were defined per WHO guidelines as any suspected or probable cases with a positive laboratory result (detection of virus RNA by RT-PCR or detection of IgM antibodies directed against Ebola virus). PCR was performed by national and international laboratories in the Guinean national surveillance network and was conducted independently of the trial. Retained specimens from EVD cases were obtained by the study team for repeat testing at the European Mobile Laboratory (EML). Aliquots for repeat testing were obtained from 79% (93/117) of EVD index cases and 88% (30/34) of confirmed EVD outcome cases with onset 10 or more days after randomization, and 80% (57/71) of all confirmed EVD outcome cases with onset less than 10 days after randomization. A total of five suspected EVD cases initially considered as index cases were negative on confirmatory testing by EML; the corresponding clusters were excluded from efficacy analyses. Test results generated by the Guinean national surveillance network laboratories represented the primary laboratory confirmation for purposes of the study analyses.

Reviewer's comment: Active surveillance for EVD cases was conducted by the Guinean MOH independent of the study sponsor for 21 days for contacts of EVD cases. This study procedure addresses some concern regarding ascertainment bias, as daily surveillance for EVD was done for all contacts independent of the study sponsor, although the open-label design of the study would allow for the surveillance team to be aware of the vaccination status of each cluster. Independent active surveillance for EVD may also address some concern regarding performance bias, as each treatment group would have access to medical personnel for the first 21 days after exposure.

As surveillance and reporting of EVD cases was conducted independently of the study, information regarding EVD status was available for each of the 11,841 contacts and

contacts enumerated in the rings (clusters), irrespective of whether informed consent was obtained. This was pre-specified in the protocol, study operating procedures (SOPs), and the statistical analysis plan (SAP). Multiple local and external ethics committees were involved in the review of study documents.

Of note, only positive PCR tests for Ebola underwent confirmatory testing. Thus, it is possible that cases of EVD were missed if negative tests were falsely negative. In response to an IR, the Applicant indicated that that there were 107 total tests completed on 38 subjects in the immediate study arm, including 18 negative tests and 89 positive tests. A total of 118 tests were completed on 50 subjects in the delayed study arm, including 14 negative tests and 104 positive tests. Between one and five tests per subject were performed, depending upon the disease progression, with survivors generally having more sequential test results than subjects that died. The proportion of negative tests was comparable in the immediate and delayed clusters, 18 (16.8%) and 14 (11.9%), respectively, suggesting that any risk of bias due to false negative testing would be evenly distributed across the study groups.

Safety surveillance

Subjects were monitored both actively and passively for a total of 84 days post-vaccination, including the following assessments:

- monitoring for 30 minutes post vaccination for immediate reaction;
- home visits on Days, 3, 14, 21, 42, 63, and 84 for occurrence of SAEs;
- collection of AEs (solicited and unsolicited) through Day 14; and
- passive reporting by telephone to a designated community leader.

Reviewer's comment: Adverse events were not coded using the Medical Dictionary for Regulatory Activities (MedDRA) until the original study datasets were converted to Study data tabulation model (SDTM) format. Thus, there are minor discrepancies between the safety data terminology for AEs in the CSR and the SDTM datasets. For the purposes of this review, the SDTM datasets served as the reference for SAE analyses.

6.1.8 Endpoints and Criteria for Study Success

Effectiveness

Primary endpoints:

- Any probable or suspected case (see definitions below) from which a blood sample taken was laboratory confirmed as positive for EVD, or
- Any deceased individual with probable EVD, from which a post-mortem sample taken within 48 hours after death was laboratory confirmed as positive for EVD.

Secondary endpoints:

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.

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.

Safety
The primary safety endpoint was based on the evaluation of SAEs to 84 days, with active monitoring of solicited and unsolicited AEs through scheduled home visits at Day 0 (vaccination), Day 3, Day 14, Day 21, Day 42, Day 63 and Day 84.

Reviewer comment: Interpretation of the safety data is limited by a lack of a placebo control or active comparator arm, an open-label study design, and a lack of prespecified causality and severity assessments.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample size
In the most likely scenario assuming an attack rate of 2% and a true vaccine efficacy of 70%, 95 rings were required in each arm to demonstrate efficacy.

Interim analysis
An interim analysis was planned after enrollment of approximately 100 rings and occurred after randomization of 98 clusters. At each interim analysis, the trial could be stopped due to early evidence of success if the p-value crossed the rejection boundary. The prespecified α spending criterion was 0.0027.

Missing data
Dropouts were censored on their date of dropping out. No imputation was performed on missing data.

Randomization
Randomization was at the level of the ring. Entire rings were randomized to immediate or delayed vaccination.

Efficacy analysis
The original SAP included an estimation of vaccine efficacy using a hazard ratio estimated using a mixed-effects, time-dependent, Cox regression model with a random effect (frailty) for the vaccination ring. However, the Cox regression model could not be used, since no EVD case was observed in the immediate vaccination clusters.

- For the estimation of vaccine efficacy with a 95% CI, a β-binomial distribution was fitted to the cluster-level numerators and denominators and using an inverted likelihood ratio test to identify the lower bound for vaccine effect.
- Fisher's exact test was used to compare the proportions of clusters with at least one event across the two trial groups.

Time period for efficacy analyses
The time period for the efficacy analyses included D and 21+D days, where D was assigned a value of 10 days to represent the incubation period of Ebola virus, the time between onset of symptoms and laboratory confirmation, and the unknown period between vaccination and a vaccine-induced protective immune response. The time period for the efficacy analyses included events of EVD occurring Day 10 to 31 post-randomization of the cluster. Events occurring in the immediate vaccination clusters <10 days after randomization were censored to account for the incubation and vaccine ramp-up periods. Events in the delayed vaccination clusters occurring <10 days after randomization were censored to maintain the comparability of the populations with

respect to exposure to the index case. Cases occurring more than 31 days post-randomization in the delayed vaccination clusters were also censored to account for vaccination on Day 21. The timing of onset of EVD cases was defined as the time of symptom onset.

Reviewer's comment: The time period for the efficacy analyses was not prospectively determined. The decision regarding the analysis period was submitted as an amendment to the Statistical Analysis Plan (SAP) after the study had begun. In the CSR, the time period of the primary analysis is relative to the time of randomization of the cluster, although the reference start time as described in the SAP amendment is relative to the time of first vaccination in the immediate clusters and the time of first enrollment in the delayed vaccination clusters. In response to an IR, the Applicant clarified that the reference start time used for efficacy analyses was the randomization of the cluster. As the date of randomization in an immediate cluster may have preceded vaccination of some individual subjects by several days in the immediate vaccination clusters, and a common cluster Day 0 was assigned by the date of randomization of the ring, some individual subjects would enter the primary analysis period fewer than 10 days after vaccination, which would have biased toward the null hypothesis.

Analysis populations
See Section 6.1.10.1

Reviewer's comment: Please see the clinical statistical review for additional details on the statistical considerations for V920-010.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed
All Vaccinated Subjects was the population used for the analysis of safety data in this trial, which consisted of all subjects who received at least one dose of study vaccine.

Subject populations for analysis were not defined in the protocol. The SAP proposed analytical strategies for the primary and secondary objectives but did not explicitly define the intent-to treat (ITT) and per protocol (PP) comparison groups. The ITT and PP analysis populations were defined in an amendment to the SAP. The primary efficacy analysis utilized the PP population, including all subjects vaccinated in the immediate arm versus all subjects who were eligible and consented on Day 0 in the delayed arm. Additional efficacy analyses included all eligible subjects and all subjects randomized to the immediate and delayed arms.

Reviewer's comment: The population selected for the primary efficacy analysis was not prospectively identified. The PP population was selected for the primary analysis to assess the effect of vaccination on EVD, whereas including all eligible or randomized subjects in each group allowed for assessment of the overall vaccination strategy. The major difference between the study population used for the primary efficacy analysis and the full set of subjects vaccinated in the study is that the primary efficacy analysis excluded subjects in the delayed treatment arm who consented on Day 21 as opposed to Day 0. The decision to exclude subjects in the delayed arm who consented on Day 21 from the primary efficacy analysis was intended to reduce any potential bias that inclusion of subjects who did not immediately consent may introduce.

In general, the enrolled population adequately represented the broader population targeted by the proposed indication, as the majority of people at risk for Ebola infection reside in regions of West Africa where Ebola epidemics have occurred.

6.1.10.1.1 Demographics
The demographics of the index cases is described in the following table.

Table 7 Demographics of index Ebola cases used to define clusters

Index case	Randomized to Immediate Vaccination (51 clusters)	Randomized to Delayed Vaccination (47 clusters)	Not randomized (19 clusters)	All clusters (117 clusters)
Median age (years)	35	35	23	35
Females	52.9%	66%	63.2%	59.8%
Dead at time of randomization	58.8%	68.1%	47.4%	60.7%
Time from symptom onset to hospitalization in days (SD)	3.9 (2.9)	3.8 (2.6)	3.2 (2.4)	3.7 (2.7)
Time from symptom onset of case to randomization of cluster in days (SD)	9.7 (5.3)	11 (4.1)	-	10.3 (4.8)
Time from symptom onset to inclusion of cluster in days (SD)	9.8 (5.1)	10.9 (4.1)	7.3 (3.7)	9.9 (4.6)

SD: standard deviation
Source: Adapted from Original BLA 1251690/2; Clinical Study Report V920-010, p.75, Table 10-3

Overall, females comprised 59.8% of the index cases and 52.2% of the confirmed cases during the entire period of the outbreak in Guinea.

Of the randomized clusters, the proportion that were located in rural areas and the median number of people in each cluster were comparable between the immediate (76.5% and 80, respectively) and delayed (76.6% and 81, respectively) vaccination clusters.

Reviewer's comment: The median age was lower in the non-randomized immediate vaccination clusters due to the protocol amendment permitting the enrollment of children. The median number of people in each cluster and the number of clusters in rural areas was comparable between the randomized groups. The delayed vaccination clusters included more women and had ~1 day longer time from symptom onset of index case to randomization of the cluster. It is unclear whether these differences could impact the efficacy findings.

The average cluster sizes including only the population used for the primary efficacy analysis was 42.2 for the immediate vaccination clusters and 30.5 for the delayed vaccination clusters (subjects consented on Day 0 only). Including subjects consenting at any time, the average cluster size in the delayed vaccination clusters was 54 individuals.

Reviewer's comment: A larger number of people per cluster in the delayed vaccination rings could increase the chance that EVD would be diagnosed in these rings, biasing the cluster-level primary statistical analysis in favor of the vaccine. However, this concern is obviated as the primary analysis included only subjects consented on Day 0, resulting in a larger number of subjects and average number of subjects per cluster randomized to

immediate vaccination (2151 and 42.2, respectively) compared to the delayed vaccination (1435 and 30.5, respectively).

The demographics of subjects by study assignment and consent status is described in the following table.

Table 8 Baseline demographic characteristics of eligible subjects and contacts with index case

	Randomized					Not randomized**		All	
	Assigned to immediate vaccination (51 clusters, n=3232)		Assigned to delayed vaccination (47 clusters, n=3096)			Assigned to immediate vaccination (19 clusters, n=2006)		All clusters (117 clusters, n=8334)	
	Consented	Not consented	Consented on visit day 0†	Consented on visit day 21†	Not consented	Consented	Not consented	Immediately vaccinated	Delayed or never vaccinated
Subject characteristics									
Number of subjects	2151	1081	1435	1104	557	1678	328	3796	4538
Age (years)	40 (29–55)	30 (25–45)	39 (27–53)	37 (27–50)	32 (23–45)	30 (22–44)	25 (18–35)	35 (25–50)	35 (25–50)
Age Group									
6 - 17	0	0	0	0	0	194 (11.6%)	78 (23.8%)	194 (5.1%)	78 (1.7%)
18 - 39	1032 (48%)	728 (67.3%)	728 (50.7%)	586 (53.1%)	357 (64.1%)	947 (5.1%)	171 (52.1%)	1958 (51.6%)	2591 (57.1)
40 – 64	889 (41.3%)	277 (25.6%)	573 (39.9%)	427 (38.7%)	168 (30.2%)	456 (27.2%)	64 (19.5%)	1336 (35.2%)	1518 (33.5%)
≥ 65 years	230 (10.7%)	76 (7.0%)	134 (9.3%))	91 (8.2%)	32 (5.7%)	81 (4.8%)	15 (4.6%)	308 (8.1%)	351 (7.7%)
Females	640/2151 (30%)	608/1081 (56%)	428/1434 (30%)	404/1104 (37%)	319/557 (57.3%)	593/1678 (35%)	179/328 (54.6%)	1223/3796 (32%)	1948/4537 (43%)
Contacts with index cases									
No detailed contact information (no consent)	0/2151 (0%)	1081/1081 (100%)	0/1435(0%)	0/1104(0%)	557/557 (100%)	0/1678(0%)	328/328 (100%)	0/3796	1966/4538 (43%)
Contact of contact‡	1727/2151 (80%)	--	1160/1435 (81%)	971/1104 (88%)	--	1418/1678 (85%)	--	3116/3796 (82%)	2160/2572 (84%)
Contact‡	424/2151 (20%)	--	275/1435 (19%)	133/1104 (12%)	--	260/1678 (15%)	--	680/3796 (18%)	412/2572 (16%)
High-risk contact‡	330/2151 (15%)	--	171/1435 (12%)	58/1104 (5%)	--	246/1678 (15%)	--	574/3796 (15%)	231/2572 (9%)

NOTE: Age Group details were added.
n=number eligible subjects in each arm
Data are median (25th quantile - 75th quantile) or n/N (%).
* Eligible subjects in randomized and non-randomized rings are included in this table.
** Six non-randomized rings included children aged 6 years and older (n=273).
† Informed consent was obtained either during the first visit (day 0) or second visit (day 21) of trial team.
‡Proportion calculated among individuals with available contact information. Two individuals were pregnant and one was severely ill.

Source: Original BLA 1251690/2; Clinical Study Report V920-010, p.77, Table 10-3

Reviewer's comment: Imbalances in some baseline characteristics may have affected the efficacy analyses. More high-risk contacts were randomized to immediate vaccination clusters (15%) compared to the delayed vaccination clusters (9%) and the subset of subjects in the delayed clusters selected for the primary efficacy analysis (consented at Day 0; 12%), which would bias the efficacy analysis against the vaccine. However, more index cases were dead at the time of randomization of the delayed vaccination clusters (68%) compared to the immediate vaccination clusters (59%), suggesting that the severity of illness may have been greater in index cases for delayed vaccination rings. Alternatively, this finding may reflect the longer time from symptom onset of case to randomization of cluster in days as seen in Table 7 above.

The age and sex distribution of subjects was generally comparable between the randomized clusters. Subjects who did not consent were similar in age and sex distribution between the immediate and delayed vaccination clusters. Compared to subjects who did consent, subjects who did not consent were younger and more likely to be women. More high-risk subjects consented on Day 0 (12% of subjects) compared to

Day 21 (5% of subjects). This may be because some high-risk subjects already had EVD by Day 21 and therefore could not consent. However, as described above, the overall proportion of high-risk subjects in the immediate vaccination clusters was higher than the delayed vaccination clusters, which could bias the analysis against the vaccine.

6.1.10.1.3 Subject Disposition

A total of 476 confirmed cases of EVD were identified as index cases. Of the 361 excluded cases, the majority (n=273; 76%) were excluded due to distance, delayed reporting, or inadequate team capacity. Rings were defined for the remaining 115 cases and for 2 additional cases from Sierra Leone (non-randomized), for a total of 117 rings comprising a total population of 11,841 CCCs.

Reviewer's comment: Limited information is provided on index cases excluded from the study.

Analysis populations: The disposition of CCCs is presented in the following table.

Table 9 Disposition of subjects

Subject description	**Allocated to immediate vaccination Subjects (rings)**	**Allocated to delayed vaccination Subjects (rings)**	**Not randomized immediate vaccination Subjects (rings)**	**Total Subjects (rings)**
Ineligible	1307 (50)	1461 (47)	739 (19)	3507 (116)
Below minimum age[1]	1141 (49)	1332 (47)	321 (17)	2794 (113)
Pregnant	7 (6)	8 (5)		15 (11)
Lactating	11 (6)	14 (7)		25 (13)
Immunosuppressed			2 (2)	2 (2)
Severe illness	3 (3)	1 (1)		4 (4)
Anaphylaxis	1 (1)			1 (1)
Missing CRF[2]	145 (23)	106 (10)	416 (13)	667 (46)
Eligible	**3232 (51)**	**3096 (47)**	**2006 (19)**	**8334 (117)**
Eligible and no consent	1081 (46)	557 (35)	328 (10)	1966 (93)
No consent given	728 (35)	441 (30)	165 (7)	1334 (72)
Absent	353 (26)	116 (18)	163 (8)	632 (52)
Eligible and consented	**2151 (51)**	**2539 (47)**	**1678 (19)**	**6368 (117)**
Consented <10 days after randomization[3]	2151 (51)	1435 (46)	1536 (19)	5122 (116)
Consented ≥10 days after randomization[3]		1104 (45)	142 (2)	1246 (47)
Not vaccinated	**32 (8)**	**498 (46)**	**1 (1)**	**531 (55)**
Withdrew consent	31 (8)	347 (39)		378 (47)
Absent	1 (1)	136 (31)		137 (32)
Suspected or confirmed EVD		12 (8)		12 (8)
Pregnant		2 (2)		2 (2)
Severe illness		1 (1)	1 (1)	2 (2)
Vaccinated	**2119 (51)**	**2041 (47)**	**1677 (19)**	**5837 (117)**

[1] minimum age is 18 years of age for pilot and randomized rings and 6 years of age for non-randomized rings.
[2] subjects without case-reporting form
[3] for non-randomized rings, the time from inclusion of the ring to consent of participant is used

Source: Adapted from Original BLA 1251690/2; Clinical Study Report V920-010, p.67, Table 10-1

To assess potential sources of bias, the Applicant compared the immediate and delayed clusters with respect to eligibility, consent, and vaccination rates.

- Ineligibility: In the 51 clusters allocated to immediate vaccination, 1307 individuals were not eligible for vaccination. Of these ineligible individuals, six (0.46%) had onset of EVD <10 days from randomization and three (0.2%) had onset ≥10 days from randomization. In the 47 clusters allocated to delayed vaccination, 1461 individuals were not eligible. Of these individuals, seven (0.5%) had onset of EVD <10 days from randomization and six (0.4%) had onset ≥10 days from randomization.

Reviewer's comment: The reasons for ineligibility and frequency of EVD cases were generally comparable among ineligible subjects randomized to immediate and delayed clusters.

- Consent of eligible subjects: The mean time from randomization to consent was comparable between the immediate clusters (1.5 days) and the subjects in the delayed clusters who consented at Day 0 (1.7 days). In the immediate vaccination clusters, 3232 individuals were eligible for vaccination, 1081 (33%) of whom were not consented, including 728 subjects who did not consent and 353 subjects who were absent. In the delayed vaccination clusters, 3096 individuals were eligible for vaccination, 557 of whom were not consented (18%), including 441 subjects who did not consent and 116 subjects who were absent. Of the 1435 subjects in the delayed vaccination clusters who consented on Day 0, 347 (24%) withdrew consent prior to vaccination, compared to 31 subjects (1.5%) who withdrew consent prior to vaccination in the immediate vaccination clusters and three subjects (0.2%) in the delayed vaccination clusters who consented on Day 21. Of note, many subjects were re-consented due to issues with the informed consent documents, so many subjects were assigned a consent date of Day 21 even if they did sign an informed consent on Day 0. Of the 2539 consenting subjects randomized to delayed vaccination, 1104 (43%) provided consent on Day 21, thus excluding them from the primary VE analysis.

Reviewer's comment: The proportion of randomized subjects who were eligible but did not consent on Day 0 was higher in the delayed vaccination clusters compared to the immediate vaccination clusters (54% versus 33%). As the second opportunity to consent may have been influenced by a survivor effect, it is appropriate that the primary efficacy analysis excluded this population.

It is notable that 24% of subjects in clusters randomized to delayed vaccination withdrew consent prior to vaccination. Of the 344 eligible subjects in clusters randomized to delayed vaccination who withdrew consent, approximately 10% were high-risk contacts, which is consistent with the overall number of high-risk subjects in the delayed and never vaccinated group (Table 8), and none developed EVD. Withdrawal of consent may represent consent bias due to the open-label study design, wherein subjects may not continue to participate once they know the treatment assignment.

- Overall vaccination of eligible and consented subjects: Of the 2151 subjects who were eligible and consented in the immediate vaccination clusters, 2119 (98%) were vaccinated. Of the 2539 subjects who were eligible and consented in the

delayed vaccination clusters, 2041 (80%) were vaccinated. By type of contact, the vaccination rate of eligible and consented subjects in the delayed vaccination clusters were: 81% of contacts of contact, 83% of non-high-risk contacts, and 73% of high-risk contacts.

Reviewer's comment: The lower rate of vaccination in the delayed vaccination clusters is primarily due to the higher rate of consent withdrawal as described above, as well as subjects who were absent at the time of vaccination. The lower rate of vaccination in the delayed vaccination clusters would not affect the primary efficacy analysis but may have decreased the study power slightly.

Compliance with safety follow up: Compliance with follow-up visits was between 83% and 97.8% for all visits in the immediate and delayed vaccination clusters. Compliance was above 89% or above for all visits with the exception of the subjects in clusters randomized to immediate vaccination or delayed vaccination clusters (consent on Day 0) on Days 14 and Day 21, when follow-up visits were cancelled in some rings due to public security issues.

Protocol deviations: A total of 55 protocol deviation reports were completed, impacting at least 819 subjects (12.9% of all eligible and consented subjects). Protocol deviations leading to elimination from analysis were reviewed. These deviations included falsified Day 3 data for 47 subjects (Day 3 assessments were conducted at the Day 14 visit) and data for ring 82 (the second confirmatory PCR test of the index case was negative). Protocol deviations not leading to elimination from analyses were also reviewed. These deviations involved ICFs, eligibility criteria, out of window study visits, late reporting of safety events, as well as various recording, reporting, documentation, and technical deviations.

Reviewer's comment: The Applicant's documentation of the events leading to subject exclusion from analyses and protocol deviations not leading to exclusion from analyses were reviewed and found to be acceptable.

6.1.11 Efficacy Analyses

The following table describes the overall number of EVD cases observed for all subjects identified for inclusion in a cluster, regardless of eligibility.

Table 10 Number of overall EVD cases by eligibility, randomization, and vaccination status

Time to onset since randomization	**Eligible CCCs IV group** Vaccinated **(n= 2119)**	**Eligible CCCs IV Group** Never vaccinated **(n= 1113)**	**Eligible CCCs DV Group** All **(n= 3096)**	**Eligible CCCs NR** Vaccinated **(n= 1677)**	**Eligible CCCs NR** Never vaccinated **(n= 329)**	**Non-eligible CCCs IV group** All **(n= 1307)**	**Non-eligible CCCs DV group** All **(n= 1461)**	**Non-eligible CCCs NR** All **(n= 739)**
<10 days	11/2119 (0.5%)	9/1113 (0.8%)	21/3096 (0.7%)	10/1677 (0.6%)	1/329 (0.3%)	6/1307 (0.5%)	7/1461 (0.5%)	6/739 (0.8%)
≥10 days	0/2108 (0%)	7/1104 (0.6%)	16/3075 (0.5%)	0/1667 (0%)	0/328 (0%)	3/1301 (0.2%)	6/1454 (0.4%)	2/733 (0.3%)
Total	11/2119 (0.5%)	16/1113 (1.4%)	37/3096 (1.2%)	10/1677 (0.6%)	1/329 (0.3%)	9/1307 (0.7%)	13/1461 (0.9%)	8/739 (1.1%)

IV group: Immediate Vaccination group; DV group: Delayed Vaccination group; NR: Not randomized

Source: Adapted from Original BLA 1251690/2; Clinical Study Report V920-010, p.102, Table 14-1

Reviewer's comment: The comparison of attack rates across the randomized treatment groups helps to assess for the presence of any imbalance in risk that would bias the primary efficacy analysis. In the 0-9 days after randomization, EVD attack rates were generally comparable (0.5% to 0.8%) between the subjects in the immediate and delayed clusters, regardless of vaccination status or eligibility. For the time period ≥10 days after randomization, EVD attack rates for subjects allocated to delayed vaccination or not vaccinated in the immediate clusters were also comparable, suggesting that the risk of EVD was similar across study groups.

Table 11 Distribution of all confirmed EVD cases among all eligible CCCs by informed consent status, randomization, and time to onset of EVD since randomization

EVD cases Time from randomization and type of contact	IV group consented (n= 2151)	IV group not consented (n= 1081)	DV group consented Day 0 (n= 1435)	DV group consented Day 21 (n= 1104)	Delayed not consented (n= 557)	NR consented (n= 1678)	NR not consented (n= 328)
Total <10 days	11 (0.5%)	9 (0.8%)	6 (0.4%)	0 (0)	15 (2.7%)	10 (0.6%)	1 (0.3%)
<10 days Contact of contacts	1	-	0 (0)	0 (0)	-	-	-
<10 days Contact	10 (all high-risk)	-	6 (5 high-risk)	0 (0)	-	10 (all high-risk)	-
Total ≥10 days	0 (0)	7 (0.6%)	10 (0.7%)	1 (0.1%)	5 (0.9%)	0 (0)	0 (0)
≥10 days Contact of contact	0 (0)	-	3	1	-	0 (0)	-
≥10 days Contact	0 (0)	-	7 (1 high-risk)	0 (0)	-	0 (0)	-

IV group: Immediate Vaccination group; DV group: Delayed Vaccination group; NR: Not randomized
Subjects who were not consented do not have information on the type of contact.
Source: Adapted from Original BLA 1251690/2; Clinical Study Report V920-010, p.83-84, Table 10-9

There were no EVD cases after 32 days post-randomization in randomized and non-randomized clusters in vaccinated and non-vaccinated individuals. Among the 11 cases of EVD in consented subjects in the delayed vaccination clusters, 4 occurred <10 days after vaccination (0, 2, 6, and 6 days post-vaccination, respectively).

Reviewer's comment: As expected, almost all EVD cases with onset <10 days after randomization occurred in high-risk contacts in both the immediate and delayed vaccination clusters. All CCCs in the same cluster were assigned the same time 0 as described above; however, the timing of exposure to Ebola may have differed between contacts and contacts of contacts. This raises the possibility that some contacts with higher risk exposures may have been infected with Ebola prior to randomization.

In the delayed clusters, an increased incidence of EVD within 10 days of randomization was observed in unconsented eligible individuals (15 cases in 557 subjects; 2.7%) compared to consented eligible subjects (six cases in 2539 subjects; 0.2%). In contrast, in the immediate clusters, the incidence of EVD within 10 days of randomization was comparable between unconsented eligible individuals (nine cases in 1081 subjects; 0.8%) and consented eligible subjects (11 cases in 2151 subjects; 0.5%). The source of

the difference in the incidence of EVD in the unconsented eligible individuals in the delayed vaccination clusters compared to other groups is unclear; however, including the group of subjects in the delayed vaccination clusters that consented at Day 21 in the primary efficacy analysis would necessarily exclude subjects who had EVD prior to the opportunity to consent at Day 21. Therefore, to eliminate any bias this may introduce, it is appropriate that the primary efficacy analysis excludes subjects who consented after Day 0.

6.1.11.1 Analyses of Primary Endpoint(s)

In the primary efficacy analysis (all vaccinated subjects in the immediate clusters versus all subjects who were eligible and consented at Day 0 in the delayed clusters during the time period of day 10 and 31 post-randomization of the clusters, no cases of confirmed EVD were observed in the immediate clusters (n= 2108; 51 clusters) and a total of ten confirmed EVD cases (attack rate 0.7%) were observed in four rings in the delayed clusters (n= 1429; 46 clusters), resulting in a vaccine efficacy (VE) of 100% (95% CI: 63.5, 100; p=0.0471).

Largely due to clustering of six confirmed endpoint EVD cases in one of the rings, the calculated intra-class correlation coefficient (ICC) was higher (0.14) than the ICC value of 0.05 that was used to estimate the trial sample size and power calculation.

Reviewer's comment: VE of 100% was observed. It is notable that the circulating strain during the 2014-2016 outbreak was an EBOV Makona strain and the V920 GP insert is based on the Kikwit strain, suggesting that protection conferred by the vaccine is not strain-specific. important considerations in the interpretation of the primary efficacy analysis include:

- *As described in publications of the results of V920-010 (Henao-Restrepo 2017), the decision was made by the DSMB to end the randomized portion of the study after an interim analysis demonstrated 100% efficacy of the vaccine. However, according to Fisher's exact test comparing the proportions of clusters with one or more eligible case, the p value for the VE calculations was 0.0036 and did not meet the prespecified criterion for success of p=0.0027. In the final primary efficacy analysis presented in the CSR, the confidence intervals and p-values were not calculated using the pre-planned alpha-spending approach.*
- *Approaches to address potential sources of bias as described above were addressed in the study design and study procedures and in secondary analyses as described below in Section 6.1.11.2 (Analyses of Secondary Endpoints). However, the full impact of potential biases, including imbalances in risk and exposure to Ebola at the cluster level, selection/consent bias, ascertainment bias, and performance bias, on the interpretation of VE data cannot be conclusively assessed. The decision to limit the delayed vaccination population to those who were eligible and consented on Day 0 was not pre-specified but is appropriate.*
- *There were 6 confirmed endpoint cases of EVD in one of the clusters in the delayed clusters. An imbalance in the distribution of super spreaders could make interpretation of the efficacy data more difficult.*
- *The efficacy of the vaccine with respect to the exact timing of Ebola virus exposure is unknown. Of the 10 EVD cases in the delayed vaccination clusters contributing to the primary efficacy analysis, seven were reported in contacts; considering the 10 to 11-day delay from index case symptom onset to*

randomization of the ring, it is possible that some contacts were already exposed prior to vaccination.

- *The analysis period is limited to 21 days; thus, conclusions about the durability of protection cannot be made.*
- *As no cases were observed more than 32 days post-randomization in randomized and non-randomized clusters in vaccinated and non-vaccinated individuals, the lack of any EVD cases ≥10 days after vaccination may be somewhat attributable to a waning epidemic; in an ongoing epidemic, a VE of 100% may not be observed.*

Per the Statistical reviewer, the 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. To estimate VE at the ring level the Statistical Reviewer compared the proportions of rings with at least one event between the two trial arms (0⁄51 vs. 4⁄46) assuming an intra-class correlation = 1 in the applicant's model, which resulted in VE of 100% (95% CI: 15.5, 100) with a p-value of 0.047 for testing the null hypothesis. To estimate VE at the subject level the Statistical Reviewer compared the proportions of events between the two trial arms (0⁄2108 vs. 10⁄1429); assuming an intra-class correlation = 0 in the applicant's mode, which resulted in VE of 100% (95% CI: 76.5, 100) with a p-value of 0.00011 for testing the null hypothesis.

6.1.11.2 Analyses of Secondary Endpoints

Planned secondary analyses included overall vaccine effectiveness against EVD, vaccine efficacy for preventing death, vaccine effect against probable and suspected cases, and estimation of EVD transmission parameters. The estimation of EVD transmission parameters is ongoing and was not included in the BLA. Due to the near-universal testing for EVD during the outbreak (26 of 502 [5%] cases did not have a definitive diagnosis), the analysis of VE against probable and suspected cases was not conducted.

The outcome of the primary efficacy analysis (column 1) and seven additional vaccine efficacy analyses (columns 2-8) are described in the following table:

Table 12 Vaccine effect on EVD cases for different comparisons of study population

	1	2	3	4	5	6	7	8
	All vaccinated in immediate (A) versus all eligible and consented on Day 0 visit in delayed (B)	All vaccinated in immediate (A) versus all eligible in delayed (B)	All eligible in immediate (A) versus all eligible delayed (B)	All CCCs in immediate (A) versus all CCCs in delayed (B)	All immediately vaccinated (A) versus all CCCs in delayed clusters plus all never vaccinated in immediate or non-randomized (B)	All vaccinated in immediate (A) versus all eligible in delayed plus all eligible never vaccinated in immediate (B)	All contacts and contacts of contacts in immediate (A) versus delayed (B)	All vaccinated in immediate (A) versus all eligible never vaccinated in immediate (B)
Group A								
Subject (clusters)	2108 (51)	2108 (51)	3212 (51)	4513 (51)	3775 (70)	3775 (70)	7241 (70)	3775 (70)
EVD cases (clusters affected)	0 (0)	0 (0)	7 (4)	10 (5)	0 (0)	0 (0)	12 (7)	0 (0)
Attack rate	0%	0%	0.22%	0.22%	0%	0%	0.17%	0%
Group B								
Subject (clusters)	1429 (46)	3075 (47)	3075 (47)	4529 (47)	7995 (116)	4507 (104)	4529 (47)	1432 (57)
EVD cases (clusters affected)	10 (4)	16 (7)	16 (7)	22 (8)	34 (15)	23 (11)	22 (8)	7 (4)
Attack rate	0.7%	0.52%	0.52%	0.49%	0.43%	0.51%	0.49%	0.49%
Vaccine effect								
Vaccine effect and 95%CI†	100% (63.5 to 100)	100% (68.9 to 100)	64.6% (-46.5 to 91.4)	64.6% (-44.2 to 91.3)	100% (77.0 to 100)	100% (79.3 to 100)	70.1% (-4.9 to 91.5)	100% (-51.5 to 100)
p value‡	0.0471	0.0045	0.344	0.3761	0.0012	0.0033	0.2759	0.125

Columns 1-4 include vaccinated subjects randomized to immediate vaccination and columns 5-8 include subjects randomized and non-randomized subjects in the immediate vaccination clusters
Source: Adapted from Original BLA 1251690/2; Clinical Study Report V920-010, p.87, Table 11-1

Efficacy analyses including randomized subjects
To assess efficacy independent of consent status in the delayed vaccination clusters, an analysis was conducted to compare all eligible subjects in the delayed vaccination clusters to all vaccinated subjects in the immediate vaccination clusters (Column 2; Table 12). The calculated VE was comparable to the primary analysis (VE 100%; 95% CI: 68.9, 100); this analysis included six additional cases of EVD, five of which were reported by subjects who did not consent.

Reviewer's comment: As subjects in the delayed vaccination clusters were given multiple opportunities to consent, it is not possible to conduct an intent to treat analysis of all consented subjects in the immediate and delayed clusters, as 5 subjects who did not consent at Day 0 had EVD and thus were excluded from consent at Day 21.

Columns 3 and 4 of Table 12 describe analyses that were conducted to assess the overall vaccine effect on EVD cases, regardless of vaccination status, in the randomized clusters. In analyses comparing all eligible subjects in the immediate and delayed vaccination clusters (Column 3) and comparing all randomized CCCs in the immediate and delayed vaccination clusters, regardless of eligibility (Column 4), the VE was 64.6% for both analyses, with CI that included 0 and p values >0.05. At the cluster level, 65.6% of subjects received V920.

Efficacy analyses including randomized and non-randomized subjects
Columns 5, 6, 7, and 8 of Table 12 describe analyses that include subjects who were immediately vaccinated in the non-randomized clusters in assessments of VE. Similar to the analyses including only the randomized populations, VE of 100% with p value <0.05 was demonstrated when all subjects who were immediately vaccinated were compared to all CCCs who were not vaccinated (Column 5; 95% CI: 77, 100) and to all eligible, randomized subjects who were not vaccinated (Column 6; 95% CI: 79.3, 100). In an

analysis comparing all CCCs allocated to immediate vaccination to all CCCs allocated to delayed vaccination, regardless of actual vaccination status, the VE was 70.1% (Column 7; 95% CI: -4.9, 91.5). Within the immediate vaccination clusters, an analysis comparing all eligible vaccinated subjects to all eligible unvaccinated subjects demonstrated a VE of 100% (Column 8; 95% CI: -51.5, 100).

Reviewer's comment: With the exception of the comparison of vaccinated and unvaccinated subjects within the clusters randomized to immediate vaccination, all efficacy analyses that considered vaccination status demonstrated a statistically significant VE of 100%. The comparison of subjects within the immediate vaccination clusters may have been underpowered to detect a difference. The attack rate of eligible but not vaccinated subjects in the immediate vaccination clusters was 0.49%, which is comparable to the attack rate of 0.52% for all eligible subjects in the delayed vaccination clusters; this may suggest that performance bias (i.e. the presence of study personnel in the communities of the immediate clusters) did not result in differential EVD risk between the treatment groups.

In analyses that assessed VE by comparing immediate and delayed vaccination clusters by eligibility and treatment allocation status independent of vaccination status, the VE was lower (64.6% to 70.1%), with CI that included 0 and p values that were all >0.05, which may reflect deficiencies in the vaccination strategy or the lack of power in the study to detect the overall VE of the vaccination strategy.

The lack of EVD cases reported in both vaccinated and unvaccinated subjects after Day 32 post-randomization may reflect the success of the vaccination strategy, waning of the epidemic independent of the vaccination strategy, or a combination of both factors.

Vaccine efficacy for preventing death
Using the same analysis period as the primary efficacy analysis, a comparison between the number of deaths in all vaccinated subjects in the randomized immediate vaccination clusters (0 deaths in 2108 subjects) and all eligible subjects in the delayed vaccination clusters who consented on Day 0 (8 deaths in 1429 subjects) yielded a vaccine effect of 100% (95% CI: 64.3, 100%, p=0.0471) against death from EVD. A comparison between the number of deaths in all vaccinated subjects in the randomized immediate vaccination clusters (0 deaths in 2108 subjects) and all eligible subjects in the delayed vaccination clusters, regardless of consent (12 deaths in 3075 subjects), yielded a vaccine effect of 100% (95% CI: 62.6, 100%, p=0.0102) against death from EVD. Assessment of vaccine effect on EVD death independent of vaccination status in the randomized clusters yielded a vaccine effect of 92% (95% CI: 23.4, 99.2%; p= 0.0525) when all eligible subjects in the immediate and delayed vaccination clusters were compared and a vaccine effect of 88.8% (95% CI: 27.6, 98.3%, p= 0.148) when all subjects randomized to the immediate and delayed vaccination clusters were compared, independent of eligibility.

Similar findings of vaccine effect on death were observed in analyses including the non-randomized subjects.

Reviewer's comment: As expected, the vaccine effect on deaths was similar to the VE for EVD disease, with wider confidence intervals and higher p-values observed in the analyses conducted independent of vaccination status.

Persistence of efficacy
The duration of protection was not assessed in this study.

Reviewer's comment: V920-010 was not designed to assess the durability of protection from EVD. The available data supports the efficacy of the vaccine in the context of protection only during the limited time period during which cases were included in the efficacy analysis. The efficacy of the vaccine to prevent EVD after this time period remains unknown.

6.1.11.3 Subpopulation Analyses
Subpopulation analyses were conducted for the primary efficacy analysis population.

Of the 2108 subjects in the immediate vaccination clusters, 70.4% were male, 29.6% were female, 76.7% were between 18 and 55 years of age, and 23.3% were >55 years of age. Of the 1429 subjects in the delayed vaccination clusters, 70.3% were male, 29.7% were female, 80.3% were between 18 and 55 years of age, and 19.7% were >55 years of age. Vaccine efficacy was 100% for all subgroups, with the following 95% CI for each subgroup: males (95% CI: 52.1, 100), females (95% CI: 30.4, 100), 18-55 years of age (95% CI: 49.9, 100), and >55 years of age (41.2, 100).

Reviewer's comment: As there were no cases in the immediate vaccination clusters in the primary efficacy analysis, further analyses by subgroup are unlikely to be informative as the VE will remain 100% and variability in the 95% CI will most likely reflect that the study is underpowered to detect a difference in VE between subgroups. Of the 10 subjects with EVD ≥10 days after randomization in the delayed group in the primary analysis, 3 were women and 7 were men.

6.1.11.4 Dropouts and/or Discontinuations
Due to the independent collection of EVD events by the MOH in Guinea, all cases of EVD were counted for the purposes of assessing efficacy. Thus, subject dropouts and discontinuations were not a factor in the analysis of efficacy. Discontinuations due to adverse events were limited to reports of EVD.

6.1.12 Safety Analyses

6.1.12.1 Methods
A total of 11,841 subjects were enrolled in V920-010: 4,539 subjects into the immediate vaccination clusters, 4,557 subjects into the delayed vaccination clusters, and 2,745 subjects into the nonrandomized clusters. A total of 5,837 enrolled subjects were vaccinated, including 194 children 6 to 17 years of age (a population that became eligible for participation in protocol version 4.0). All Vaccinated Subjects was the population used for the analysis of safety data in this trial, which consisted of all subjects who received at least 1 dose of study vaccine (n= 5,837).

Approximately 90% of all vaccinated subjects were compliant with safety follow-up visits through 84 days post-vaccination. At each visit day, compliance with follow up was between 86.3% and 93.4% in the immediate vaccination clusters, 83% to 95.1% in the delayed vaccination clusters, and between 92.9% to 97.8% in the non-randomized clusters.

Safety monitoring procedures included observation for a 30-minute post-vaccination period, contact on Days 3 and 14 for the assessment of solicited injection site (pain and induration) and systemic (fever, muscle pain, fatigue, vomiting, diarrhea, headache, arthralgia, and myalgia) AEs, unsolicited AEs, and SAEs, and contact on Days 21, 42, 63, and 84 for the assessment of SAEs. Only SAEs were assessed for causality. At Days 3, 14, 21, 42, 63, and 84 post-vaccination (safety follow-up home visits), each subject's temporal artery temperature was checked using a calibrated thermometer.

Safety data were analyzed in a separate statistical safety report submitted to the BLA. In this report, AEs were not coded using a standard medical dictionary and were described in the analysis tables using verbatim terms.

Reviewer's comment: The Applicant submitted translated French datasets to the BLA, in which the verbatim terms were coded to MedDRA terms (MedDRA version 20.0). Thus, there are differences between the translated datasets and the analyses provided in the statistical safety report. The statistical safety report analyses of solicited adverse events and SAEs were able to be reconciled with the translated datasets; however, this was not the case for unsolicited events, as described in detail below.

6.1.12.2 Overview of Adverse Events

Solicited Adverse Events (Adults)

Solicited adverse events were reported by 59.5% of vaccinated adult subjects through Day 14.

The following table describes solicited adverse event rates by time since vaccination:

Table 13 Proportion of vaccinated adults (n= 5643) reporting a solicited local or systemic adverse event by time since vaccination

Adverse Event	0-30 minutes N (%)	31 minutes- 3 days N (%)	4-14 days N (%)	Overall 0-14 days N (%)
Headache	41 (0.7)	1563 (29.1)	177 (3.5)	1690 (33.5)
Fatigue	5 (0.1)	1233 (23.0)	122 (2.2)	1301 (26.1)
Muscle pain	7 (0.1)	875 (16.3)	55 (1.1)	923 (18.6)
Arthralgia	3 (0.1)	851 (15.9)	79 (1.6)	915 (18.5)
Myalgia	6 (0.1)	816 (15.2)	47 (0.9)	857(17.3)
Injection pain	70 (1.2)	362 (6.8)	8 (0.2)	435 (8.8)
Diarrhea	0 (0)	53 (1.0)	15 (0.3)	68 (1.4)
Vomiting	0 (0)	21 (0.4)	4 (0.1)	24 (0.5)
Fever	2 (<0.1)	8 (0.1)	2 (<0.1)	12 (0.2)
Induration	0 (0)	1 (<0.1)	0 (0)	1 (<0.1)

Response rates: 0-30 minutes >99%; 31 minutes-3 days 95%; 4-14 days 90%; overall 87-88%
Source: Adapted from Original BLA 1251690/2; Statistical Safety Report V920-010, p.21, Table 4-2

Compared to other reporting periods, the proportion of subjects reporting solicited local or systemic events was highest 31 minutes to 3 days following vaccination. Solicited local events were infrequently reported (8.8% of subjects overall with injection pain and only a single subject with induration). The most commonly reported solicited systemic events included headache, fatigue, muscle pain, arthralgia, and myalgia.

Most solicited events were mild-moderate in severity (98.6%). Of the 82 severe solicited events (1.2% of total solicited events), the most frequently reported included fatigue (24% of severe events), injection pain (20.7% of severe events), and muscle pain/myalgia (22.9% of severe events).

The overall median duration of all solicited events was 2 days (Interquartile range [IQR] 1-3). The longest median durations of events were observed for severe events, including 7 days for diarrhea and 4 days for vomiting.

Solicited Adverse Events (Children)

The following table describes solicited adverse event rates in pediatric subjects by time since vaccination:

Table 14 Proportion of vaccinated children (n= 194) reporting a solicited local or systemic adverse event by time since vaccination

Adverse Event	0-30 minutes N (%)	31 minutes- 3 days N (%)	4-14 days N (%)	Overall 0-14 days N (%)
Headache	0 (0)	47 (24.9)	4 (2.2)	49 (26.3)
Fatigue	0 (0)	10 (5.3)	1 (0.5)	11 (6.0)
Injection pain	0 (0)	9 (4.8)	0 (0)	9 (5.0)
Muscle pain	0 (0)	4 (2.1)	1 (0.5)	5 (2.8)
Myalgia	0 (0)	4 (2.1)	1 (0.5)	5 (2.8)
Arthralgia	0 (0)	3 (1.6)	1 (0.5)	4 (2.2)
Fever	0 (0)	1 (0.5)	1 (0.5)	2 (1.1)
Diarrhea	0 (0)	0 (0)	1 (0.5)	1 (0.6)
Vomiting	0 (0)	1 (0.5)	0 (0)	1 (0.6)
Induration	0 (0)	0 (0)	0 (0)	0 (0)

Response rates: 0-30 minutes 100%; 31 minutes-3 days 97%; 4-14 days 96%; overall 93-96%
Source: Adapted from Original BLA 1251690/2; Statistical Safety Report V920-010, p.24, Table 4-5

Compared to other reporting periods, the proportion of pediatric subjects reporting solicited events was highest 31 minutes – 3 days following vaccination. Solicited local events were infrequently reported (5% of subjects overall with injection pain and no subjects with induration). The most commonly reported solicited systemic events included headache and fatigue.

Most solicited events were mild-moderate in severity (96.9%). One severe event of fatigue was reported.

The overall median duration of all solicited events was 2 days (Interquartile range [IQR] 1-3). The longest median duration was observed for events of arthralgia (4.5 days).

Reviewer's comment: Solicited adverse events were reported by 38.2% of children and 59.5% of adults. Headache and fatigue were the most frequently reported solicited events, regardless of age. Severe solicited events were infrequent (~1% of all events) and overall, the median duration of any type of event was < 5 days.

Unsolicited Adverse Events (Adults)

The proportion of vaccinated adults reporting any unsolicited AE was 13.3% for the 0 to 14 day reporting period. The proportion of vaccinated adult subjects reporting each

unsolicited AEs by verbatim term and by time since vaccination is summarized in the following table, as provided in the Statistical Safety Report for V920-010.

Table 15 Proportion of vaccinated adults (n= 5643) reporting an unsolicited adverse event by time since vaccination

Adverse Event	0-30 minutes N (%)	31 minutes- 3 days N (%)	4-14 days N (%)	Overall 0-14 days N (%)
Fever	2 (0)	131 (2.4)	16 (0.3)	148 (3.0)
Lumbar pain	0 (0)	82 (1.5)	34 (0.7)	113 (2.3)
Vertigo	5 (0.1)	82 (1.5)	25 (0.5)	112 (2.3)
Gastritis	1 (<0.1)	65 (1.2)	22 (0.4)	86 (1.8)
Chill	0 (0)	73 (1.4)	10 (0.2)	83 (1.7)
Abdominal pain	1 (<0.1)	34 (0.6)	13 (0.3)	47 (1.0)
Anorexia	1 (<0.1)	42 (0.8)	8 (0.2)	51 (1.0)
Other Aes	0 (0)	28 (0.6)	11 (0.2)	39 (0.9)
Nausea	2 (0)	1 (<0.1)	4 (0.1)	27 (0.6)
Cough	1 (<0.1)	14 (0.3)	11 (0.2)	25 (0.5)
Eye trouble	0 (0)	14 (0.3)	4 (0.1)	18 (0.4)
Neck pain	0 (0)	15 (0.3)	4 (0.1)	19 (0.4)
Skin pain	1 (<0.1)	7 (0.1)	11 (0.2)	19 (0.4)
Constipation	0 (0)	9 (0.2)	6 (0.1)	15 (0.3)
Hyperhidrosis	2 (0)	12 (0.2)	3 (0.1)	17 (0.3)
Sleep trouble	1 (<0.1)	11 (0.2)	2 (.1)	14 (0.3)
Boil	0 (0)	1 (<0.1)	8 (0.2)	9 (0.2)
Palpitation	1 (<0.1)	5 (0.1)	3 (0.1)	9 (0.2)
Diarrhea	0 (0)	1 (<0.1)	2 (<0.1)	3 (0.1)
Malaria	0 (0)	1 (<0.1)	4 (0.1)	5 (0.1)
Ringing ears	1 (<0.1)	3 (0.1)	3 (0.1)	7 (0.1)

Response rates: 0-30 minutes >99%; 31 minutes-3 days 95%; 4-14 days 90%; overall 87%
Source: Adapted from Original BLA 1251690/2; Statistical Safety Report V920-010, p.27, Table 4-8

Compared to other reporting periods, the proportion of subjects reporting unsolicited events was highest 31 minutes- 3 days following vaccination. Unsolicited events reported by more than 1% of subjects included chills, fever, gastritis, lumbar pain, and vertigo.

Reviewer's comment: In response to an IR regarding differences in unsolicited events between the translated datasets and the Statistical Safety Report, the Applicant stated that the differences were due to the following:

- *The Statistical Safety Report tabulated AEs by verbatim terms and the datasets coded verbatim terms to MedDRA terms.*
- *During the study, multiple AEs were documented in a free text field of the eCRF. These multiple AEs were coded to the MedDRA preferred term (PT) of "Ill-defined disorder" in the SDTM datasets. The verbatim terms classified under "Ill-defined disorder" are mapped to the variable AETERM in the ADAE dataset.*
- *Day range calculations were also handled differently between the R analyses (which treated visit as a categorical variable) and the derivations used in the SDTM dataset creations (which applied time windows around the visit to classify the continuous relative day into visits).*

In response to an IR, the Applicant provided a tabular summary of unsolicited events by maximum intensity for all vaccinated subjects based on the MedDRA coded terms from the translated datasets (ADAE); events are discussed below. It remains unclear how the

data for Table 15 above were analyzed as the verbatim terms reported in the provided datasets do not all match the reported terms, limiting the interpretability of the provided analysis.

Unsolicited Adverse Events (Children)
In the statistical safety report, a total of 8 pediatric subjects (4.4%) reported any unsolicited event, including abdominal pain (1.1% of subjects), cough (0.6% of subjects), fever (2.8% of subjects), and other events (0.6% of subjects).

Reviewer's comment: In the ADAE dataset, a total of 7 pediatric subjects with unsolicited events were identified, including abdominal pain (n= 2), feeling feverish (n= 4), cough (n= 1), and rhinorrhea (n= 1).

Unsolicited Adverse Events (All Vaccinated Subjects) from MedDRA-coded datasets, including SAEs
Based on the translated datasets using the All Subjects Vaccinated population (n= 5837 including children), unsolicited events were reported by 11.5% of subjects, 0.6% of whom reported severe AEs. Most severe events were EVD.

Unsolicited AEs reported by ≥1% of subjects included back pain (1.5% of subjects), chills (1.0% of subjects), feeling hot (1.4%), ill-defined disorder (1.7%), and vertigo (1.4%).

Reviewer's comment: As discussed above, the Applicant provided a tabular summary of unsolicited events using MedDRA PTs from the translated dataset. A total of 100 subjects were identified in the ADAE dataset with multiple verbatim adverse events in the AETERM variable. Instead of coding each event to a single MedDRA PT, these multiple events reported by a single subject were coded to the MedDRA PT of "Ill-defined disorder." In response to an IR regarding the coding strategy used for these multiple events, the Applicant indicated that sponsor collected AE data using open text fields and that open text fields listing multiple AE terms were MedDRA coded to "Ill-defined disorder". These events were not coded to individual PTs to maintain data traceability. Line listings for these 100 subjects were provided and were reviewed. Many of the reported terms reflect commonly reported events (e.g., fever, back pain, abdominal pain); thus, the proportions of subjects with specific adverse events in analyses of the ADAE dataset are likely underestimates of the actual proportion. Most events were mild, although some reports of cough, anorexia, and fever were severe.

The reporting rate for unsolicited events was low for both adults and children (13.3% and 4.4%, respectively). Safety events were collected at home visits conducted by study staff with retrospective ascertainment of interim adverse events. Diary cards were not distributed for direct recording of events by subjects, which may have decreased reporting rates. Overall, the pattern of the most frequently reported events likely reflects the safety profile for the vaccine, including fever, chills, abdominal symptoms, and vertigo; however, the lack of a comparator group confounds interpretation of the proportion of events likely to be attributable to vaccination.

6.1.12.3 Deaths
A total of 19 adult vaccinated subjects reported 20 SAEs with a fatal outcome. Of the 20 SAEs, the majority (n= 13; 65%) were EVD, all of which had onset within 10 days of vaccination. Sudden death was reported by two subjects; a concurrent event of malaria

was reported by one subject with EVD; and appendicitis, HIV infection CDC Group IV subgroup C2 and infection with tuberculosis, sudden cardiac death, and probable gastroduodenal ulcer complicated by probable tumor were reported by one subject each. None of the fatal events were considered related to vaccination. Brief narratives of fatalities that were not due to EVD are as follows:

- A 60-year old male reported an event of appendicitis on Day 60 after vaccination, after which the subject underwent an appendectomy. The subject died due to appendicitis with post-procedural complication on Day 94 after vaccination.
- An 81-year old male with a history of pyuria and hematuria was reported to experience sudden death at home on Day 85 after vaccination. No symptoms were reported in the days preceding his death. Additional information indicated that the cause of death was renal failure.
- A 41-year old male with a history of HIV diagnosed 17 days prior to randomization into the delayed arm cluster reported events of HIV CDC Group IV subgroup C2 and infection with tuberculosis. On Day 9 after vaccination, the subject had a chest x-ray with homogeneous opacities in both lung fields with lung cavities that were more pronounced on the right; he was treated with trimethoprim-sulfamethoxazole. On Day 34, the subject reported persistent fever, cough, dyspnea, and asthenia and died the following day.
- A 70-year old male with a history of inguinal hernia was reported to experience sudden death at home on Day 84 after vaccination. On Day 80, the subject reported abdominal pain; additional information from the site indicated that the subject's death was attributed to a strangulated inguinal hernia.
- A 56-year old female with a history of gastroduodenal ulcer reported symptoms of fever, chest pain, epigastralgia, anorexia, and deterioration of general condition on or about Day 64. On Day 68, the subject reported asthenia, profuse sweating, and chills, and died the same day. The death was attributed to ulceration of a gastroduodenal ulcer complicated by gastric neoplasm.
- A 53-year old male with a history of hypertension was reported to experience sudden cardiac death attributed to myocardial infarction on Day 10 after vaccination.

Reviewer's comment: In response to an IR, the Applicant provided narratives and case report forms (CRFs) for all fatal events, which were translated from the original French. There is inadequate information to assess causality for the fatal event of sudden cardiac death due to myocardial infarction; although the event is temporally related to vaccination, the limited medical history provided makes an assessment of the contribution of underlying medical conditions to the event difficult. The remaining fatal events have clear alternative or infectious etiologies and the Applicant's assessment of causality is appropriate.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 50 non-fatal SAEs were reported by 46 vaccinated subjects, including 5 SAEs reported by 4 children. SAEs reported by children included malaria (n= 2), malaria and umbilical hernia (n= 1), and EVD (n=1). The remaining 46 non-fatal SAEs included EVD (n= 15); malaria (n= 11); abortion spontaneous, anaphylactic reaction, appendicitis, infection, and pyrexia (each reported by 2 subjects); and ankle fracture, clavicle fracture, craniocerebral injury, erysipelas, HIV infection CDC Group IV subgroup C2, influenza

like illness, injury, road traffic accident, and wound infection (each reported by one subject). An additional SAE of Cesarean section was reported on Day 200.

Reviewer's comment: The SAEs above are listed by the MedDRA PT assigned in the translated datasets.

In the Statistical Safety Report, three SAEs were considered related to V920, including anaphylaxis, febrile reaction, and influenza-like illness on the day of vaccination. In the ADAE dataset and line listings provided by the sponsor in response to an IR, 6 SAEs were considered related, including additional events of anaphylaxis, pyrexia, and infection. Brief narratives of the six related SAEs are as follows:

- A 23-year old male reported an SAE of infection with onset one day after vaccination. Symptoms included headache, chills, and inguinal swelling. On Day 3, the subject had fever of 38.8ºC and was transferred to an Ebola Treatment Unit (ETU) for evaluation. Ebola PCR testing was negative, and the subject was discharged home on Day 6, at which time the subject had recovered.
- A 28-year old male reported an SAE of pyrexia and additional AEs of nausea, vomiting, anorexia, abdominal pain, and headache, and was transferred by ambulance to an ETU and hospitalized on Day 0. On Day 1, the subject experienced headache, fatigue, and myalgia. Multiple RT-PCR tests were negative for Ebola disease and a diagnostic test was negative for malaria. The subject was discharged on Day 3 and all symptoms resolved by Day 5.
- A 60-year old male reported an SAE of pyrexia on Day 2 and additional AEs of chills and asthenia. On Day 3, the subject was transferred to an ETU and hospitalized. Multiple RT-PCR tests were negative for Ebola disease and a diagnostic test was negative for malaria. On Day 7, the pyrexia resolved.
- A 60-year old female reported an SAE of influenza-like illness on Day 0. Symptoms included severe cough, anorexia, and fever (38.8°C) and the subject was admitted to the ETU. Multiple RT-PCR tests were negative for Ebola disease and a diagnostic test was negative for malaria. On Day 3, the symptoms resolved, and the subject was discharged home.

Reviewer's comment: The causality assessment for the SAEs of pyrexia, infection, and influenza-like illness are appropriate, as the reported symptoms are consistent with the vaccine reactogenicity profile. The Applicant has indicated that they do not consider the events of infection and influenza-like illness to be related, as there was insufficient information to establish a causal relationship. These events appeared to be considered serious primarily because they necessitated evaluation for EVD in the context of an ongoing outbreak; it is possible that the reported events would not be considered serious under normal circumstances.

- A 70-year old male reported an SAE of anaphylactic reaction on Day 0, 12 hours following vaccination, including symptoms of facial swelling, profuse sweating, generalized itching, and urticaria. On Day 1, an AE of arthralgia was also reported. The subject was treated with dexamethasone, hydrocortisone, promethazine, and loratadine. On Day 2, anaphylactic reaction and hypersensitivity reaction were resolved, and on Day 5, arthralgia resolved.
- A 35-year old male reported an SAE of anaphylactic reaction and allergic dermatitis on Day 0 (in the evening following vaccination) for which he was

hospitalized. Details of the anaphylactic reaction are not provided in the narrative report. The subject was treated with betamethasone and hydrocortisone. This report is confounded by concomitant use of amoxicillin for a leg wound.

Reviewer's comment: The causality assessment for the SAEs of anaphylactic reaction are appropriate as the events were temporally related to vaccination and are biologically plausible. Two events of anaphylaxis in a single study is notable; however, the lack of detail provided confounds a full assessment of these cases. It is notable that each case presented hours after vaccination, although both occurred <24 hours after vaccination. According to the Brighton Collaboration criteria for the diagnosis of anaphylaxis, multiple organ systems must be involved, including cardiovascular or respiratory symptoms. In each reported case, only dermatologic findings are reported. The second case is confounded by the concomitant use of amoxicillin, which is associated with allergic reactions. The diagnostic criteria used to inform the AE term of anaphylactic reaction is not provided in the case narratives. Product labeling will include information about these events as a Warning and Precaution, with instructions to have appropriate medical treatment and supervision available in the event of an anaphylactic reaction following V920.

The remaining SAEs were not considered related to vaccination by the Sponsor. SAEs of spontaneous abortion were reported by 2 subjects on Days 110 (at 3 months gestation) and Day 23 (unknown gestational age), respectively. Based on the limited information provided in case narratives, it is possible that the subjects were pregnant at the time of vaccination or shortly thereafter, and the impact of vaccination on the pregnancy losses is unknown.

The remaining SAEs were due to infection, injury, or anatomical defects, all of which have a plausible alternative etiology and do not appear to represent a pattern of events suggestive of a safety signal.

A total of 16 non-fatal SAEs of Ebola disease are included in the safety datasets for this BLA; however, 4 of these reports were not confirmed as Ebola. In response to an IR, the Applicant has confirmed that there are not updated PTs assigned to these events.

6.1.12.7 Dropouts and/or Discontinuations

As the vaccination is a single dose, there was no opportunity for subjects to drop out of treatment. Some subjects in the delayed clusters did not complete vaccination; however, as safety data were only collected after vaccination, it is unknown whether this was due to an AE other than EVD. As described above, compliance with safety follow-up visits was generally close to or above 90% for each group and visit.
Reviewer's comment: In the context of an ongoing outbreak, full compliance with safety follow-up may have been complicated.

6.1.13 Study Summary and Conclusions

V920-010 was a cluster randomized study of immediate and delayed vaccination against EVD. In the primary efficacy analysis (all vaccinated subjects in the immediate clusters versus all subjects who were eligible and consented at Day 0 in the delayed clusters during the time period of day 10 and 31 post-randomization of the clusters, no cases of confirmed EVD were observed in the immediate clusters (n= 2108; 51 clusters) and a

total of 10 confirmed EVD cases (attack rate 0.7%) were observed in 4 rings in the delayed clusters (n= 1429; 46 clusters), resulting in a vaccine efficacy (VE) of 100% (95% CI: 63.5, 100; p=0.0471). The results of additional efficacy analyses conducted to assess potential sources of bias were generally comparable to the primary analysis and supported the benefit of vaccination with V920. Considerations in interpretation of the VE data include potential sources of bias associated with the study design and the conduct of a study in an outbreak setting, as well as the narrow analysis window. The durability of protection from EVD was not assessed in this study.

Headache and fatigue were the most frequently reported solicited events, regardless of age. Severe solicited events were infrequent (~1% of all events) and overall, the median duration of any type of event was < 5 days. Unsolicited and serious adverse events were infrequently reported; however, interpretation of safety data is very limited due to a reliance on subject recall, lack of a comparator group, and lack of detailed SAE information. A total of six related SAEs were reported, including two events of anaphylaxis, febrile reaction, pyrexia, infection and influenza-like illness. Due to temporal association and biologic plausibility, the assessment that these SAEs were related to vaccine is appropriate.

6.2 Trial #2

V920-009: Partnership for Research on Ebola Vaccines in Liberia (PREVAIL)
First subject first visit: February 2, 2015
Date of last subject visit for 12-month timepoint: May 12, 2016
Database lock for 12-month timepoint: December 13, 2017
Estimated study completion date: June 1, 2020
Sponsor name: National Institutes of Health/National Institute of Allergy and Infectious Diseases/Office of Clinical Research Policy and Regulatory Operations

6.2.1 Objectives

The primary objective of the study was to determine the efficacy and safety of V920 as compared to placebo (pooled placebo groups).

Reviewer's comment: The study also included an arm that assessed another Ebola vaccine candidate. The study was designed to collect efficacy and safety data simultaneously for two leading Ebola vaccine candidates; data from the other candidate vaccine group is not included in the BLA. Due to the low incidence of Ebola in Liberia, there were no data available to assess the primary efficacy objective of the study. However, immunogenicity and safety data from the V920 study group and the pooled placebo groups through 12 months after vaccination are presented in the BLA. The V920-009 trial is currently ongoing in a 5-year extension to evaluate immunogenicity at Months 24, 36, 48, and 60 after vaccination.

6.2.2 Design Overview

V920-009 was originally designed as a Phase 2/3 randomized, double-blind, placebo-controlled safety and efficacy study of V920 and another Ebola vaccine candidate in adults 18 years of age and older. Study volunteers were randomized in a 2:1:2:1 ratio to receive 2 mL of an Ebola vaccine candidate, 2 mL of placebo, 1 mL of V920, or 1 mL of placebo. The trial was initially designed to be event-driven with a target of 112 primary events for each vaccine versus the pooled placebo comparison. The initial target to

recruit 600 adults to the Phase 2 sub-study was achieved in early March 2015. The Phase 2 sub-study was subsequently expanded to 1500 subjects (including 500 subjects in each vaccine group and the pooled placebo group) with follow-up for 12 months to obtain additional safety and immunogenicity data. Due to the low incidence of EVD in Liberia, enrollment ended before any subjects were enrolled in the Phase 3 portion of the trial. Thus, the CSR for this study does not include efficacy data. Safety and immunogenicity data for the 12-month period following vaccination are provided in the BLA.

Reviewer's Comment: The study is adequately designed to collect safety data that contributes to the understanding of the safety profile of V920. The immunogenicity data are considered supportive.

6.2.3 Population

Inclusion criteria: Adult ≥18 years of age who can provide informed consent and is likely to be in the surrounding area of the vaccination center for at least 1 year.

Exclusion criteria: Fever > 38ºC, history of EVD (self-report), current pregnancy (a negative urine pregnancy test was required for women of child-bearing potential), breast-feeding, any condition which would limit the ability of the participant to meet the requirements of the study protocol (e.g., any serious illness).

6.2.4 Study Treatments or Agents Mandated by the Protocol

Study participants received V920 at a nominal dose of 2×10^7 pfu (1 mL) or placebo (sterile normal saline; 1 or 2 mL). The 2 mL preparation of placebo was used as a control for the ChAd3-EBO Z vaccine, which is administered as a 2 mL dose.

6.2.5 Directions for Use

Vaccine or placebo was administered via intramuscular injection in the upper, outer aspect of the deltoid muscle.

6.2.6 Sites and Centers

This was a single center study conducted at Redemption Hospital in Monrovia, Liberia.

6.2.7 Surveillance/Monitoring

Subjects had visits at vaccination, Week 1, Week 2 (subset n=201), Month 1, Month 6, and Month 12; with additional visits at 2, 4, 8, and 10 months to assess for possible EVD and SAEs.

- Laboratory tests included chemistry (ALT, AST, chloride, creatinine, potassium, sodium), coagulation (aPTT, fibrin d-dimer), and hematology (basophils, basophils/leukocytes, eosinophils, eosinophils/leukocytes, erythrocyte mean corpuscular HB concentration, erythrocyte mean corpuscular hemoglobin, erythrocyte mean corpuscular volume, erythrocytes, erythrocytes distribution width, hematocrit, hemoglobin, leukocytes, lymphocytes, lymphocytes/leukocytes, mean platelet volume, monocytes, monocytes/leukocytes, neutrophils, neutrophils/leukocytes, platelets) collected at Vaccination, Week 1, and Month 1 visits.

- Serology tests for HIV (HIV-1 and/or 2 rapid antibody) and syphilis (treponema pallidum antibody), and chemistry test for pregnancy (choriogonadotropin beta) were performed at the Vaccination visit. Subjects were tested for Ebola Zaire Virus GP IgG antibody at Vaccination, Week 1, Month 1, Month 6, and Month 12 visits.
- Solicited local (pain and local reaction [erythema, swelling, blistering, ulceration/necrosis]) and systemic (body temperature, weight, joint problems [pain/tenderness, swelling, stiffness, redness/warmth], or targeted symptoms [feverishness, fatigue, muscle pain, headache, nausea, abnormal sweating, rash, mouth ulcers, unexplained bleeding or bruising, joint pain, or "other" symptoms]) adverse events were collected at 30 minutes, Week 1, and Month 1 following vaccination. Joint-related events were solicited at a Week 2 visit for a subset of subjects.
- Unsolicited AEs were collected at Week 1 and Month 1 after vaccination.
- SAEs were collected at Week 1, Months 1 and 2, and every 2 months through study end.

The study was monitored by an independent Data and Safety Monitoring Board (DSMB).

Reviewer's comment: A diary card was not provided and all AEs were collected verbally at study visits, which may have affected recall of events.

6.2.8 Endpoints and Criteria for Study Success

The primary objective of the study was to determine the efficacy of V920 vaccine as compared to placebo, with a primary efficacy endpoint of EVD occurring 21 days or more following randomization. As described above, enrollment in the study ended prior to initiation of the Phase 3 component due to the waning incidence of EVD. Therefore, the primary and secondary endpoints related to EVD (all-cause mortality, definite EVD occurring at any time after randomization, definite or probable EVD occurring 21 days or more following randomization, definite or probable EVD at any time after randomization, deaths attributed to definite or probable EVD, and duration of EVD for surviving participants) were not assessed. The primary safety endpoint was the occurrence of SAEs during the first 30 days after randomization. Secondary safety endpoints presented in the CSR include comparisons for the V920 and pooled placebo groups for SAEs reported at any time after randomization through 12 months after vaccination, solicited local and systemic adverse events through 1 month after vaccination, and unsolicited adverse events through 1 month after vaccination. Separate assessments of joint related symptoms at Week 1, Week 2 (subset only), and Month 1 were also provided.

Ebola-specific antibodies assessed at Week 1 and Months 1, 6, and 12 after vaccination were provided in a separate report of immunogenicity. The key immunogenicity endpoint defined in the trial protocol was Ebola-specific antibodies over 12 months following vaccination with V920. No formal hypothesis testing was conducted. The following immunogenicity endpoints were collected for the study at Months 1, 6, and 12:
GMTs and GMFRs for GP-ELISA and $PRNT_{60}$ with 95% CIs and seroresponse rates overall and for each time point with 95% CIs. Seroresponse was defined as follows:

- GP-ELISA: Primary endpoint of a ≥2-fold increase in titers from baseline and ≥200 EU/mL and a secondary endpoint: a ≥4-fold increase in titers from baseline
- PRNT: a ≥4-fold increase in titers from baseline.

Due to concerns for potential transmission of Ebola virus, immunogenicity samples underwent gamma-irradiation (50 kilograys) prior to shipping.

Reviewer comments: To align the immunogenicity reports provided in the BLA, the immunogenicity endpoints were based on the Integrated Summary of Immunogenicity Analysis Plan developed by the Applicant and were not based on the study Statistical Analysis Plan, which was developed by the study sponsor (NIH). No separate Applicant Statistical Analysis Plan for the immunogenicity analyses was provided; however, the analyses do align with other study reports in the clinical development program.

A total of 24 subjects participated in a sub-study to measure plasma levels of V920 RNA using reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays on Days 3, 10, and 14.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample size

Initial sample size calculations for the intended efficacy analysis were event-driven, with a target of 112 primary events for each vaccine versus placebo comparison. After discontinuation of the Phase 3 portion of the study, the Phase 2 sample size target was increased from N=200 to N=476 per group to provide greater power for the safety and immunogenicity outcomes. Power was 80% or greater to detect an AE that occurred in at least 4% of vaccines and no more than 1% of subjects in the pooled placebo group, or one that occurred in at least 10% of vaccine recipients and no more than 5% of those in the pooled placebo group.

Derived and transformed data

Safety data: For the analysis of solicited symptoms, missing or non-evaluable measurements were not replaced. AEs were coded using MedDRA version 20.0.

Immunogenicity data: GP-ELISA values below the lower limit of quantification (LLOQ) were imputed to one-half the value of the LLOQ. No imputation was performed for missing data. For the assessment of humoral immunogenicity, the following applied:

- For GMTs and GMFRs, data were first log-transformed. The transformed data were then analyzed by ANOVA. The ANOVA statistics were then back-transformed into GMTs and GMFRs.
- Seroresponse statistics were based on frequencies.
- Subjects with a baseline GP-ELISA titer ≥200 EU/mL were considered seropositive at baseline.

Statistical analyses

No formal hypothesis testing was conducted.

Reviewer's comment: As described in Section 6.2.8, no separate Applicant Statistical Analysis plan was submitted to the BLA. Multiple safety analyses described in the Sponsor's Statistical Analysis Plan were not conducted. In response to an IR, the Applicant provided a rationale for all safety analyses that were included in the Sponsor Statistical Analysis Plan but were not conducted (Amendment 31). In general, the analyses were changed to be consistent with other safety analyses included in the BLA. Therefore, the data captured in the analyses that were performed remained

representative of the prespecified analyses such that the analyses that were not conducted were not critical to the review of safety data.

Analysis populations
See Section 6.2.10.1 (Populations Enrolled/Analyzed).

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

The Full Analysis Set (FAS) population was used for the analysis of immunogenicity data in this trial. The FAS population consists of all randomized and vaccinated subjects with a serology assessment collected specific to each endpoint (GP-ELISA and PRNT).

Additional immunogenicity analyses were not conducted for the Per-Protocol (PP) population (all randomized and vaccinated subjects with a serology assessment collected within the allowed time window and without an important protocol deviation) as only 1 protocol deviation was identified: a female subject was determined to be pregnant after being vaccinated with placebo.

The All Subjects as Treated (ASaT) population was used for the analysis of safety data in this trial. The ASaT population consisted of all randomized subjects who received a single dose of V920 or placebo.

6.2.10.1.1 Demographics

The demographics of the treatment groups are described in the following table:

Table 16 Subject demographics

	V920 (N= 500) n (%)	**Placebo (N= 500) n (%)**	**Total (N= 1000) n (%)**
Male	313 (62.6)	323 (64.6)	636 (63.6)
Female	187 (37.4)	177 (35.4)	364 (36.4)
<18 YOA	0 (0)	2 (0.4)	2 (0.2)
18 to 65 YOA	495 (99.0)	487 (97.4)	982 (98.2)
>65 YOA	5 (1.0)	11 (2.2)	16 (1.6)
Black or African-American	500 (100.0)	500 (100.0)	1000 (100.0)

YOA: years of age
Source: Original BLA 125690/1; Clinical Study Report V920-009, p.6, Table 10-3

Mean height, weight, and BMI were comparable across the treatment groups.

Reviewer's comment: The subject demographics were comparable between the treatment and placebo groups. Of note, the two subjects identified as <18 years of age were 18 years of age at participation but are listed as <18 years due to the use of year to determine the age for the table.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Medical history conditions were similar across the V920 and placebo groups.

6.2.10.1.3 Subject Disposition

Of the 1509 subjects screened, 1500 (99.4%) were randomized and nine (0.6%) were not randomized. Of the nine subjects who were not randomized, eight were pregnant and one withdrew consent. All subjects in the V920 (n= 500) and placebo groups (n= 500) were treated as randomized. In the V920 group, 97.2% of subjects completed the study. Of the 14 subjects who did not complete the study, five died and nine were lost to follow-up. In the placebo group, 97.4% of subjects completed the study. Of the 13 subjects who did not complete the study, six died and seven were lost to follow-up. No subjects discontinued from the trial due to an AE.

FAS population for immunogenicity analyses: Of the 500 subjects who received V920, 477 had complete specimen sets available for immunogenicity testing by GP-ELISA assay and $PRNT_{60}$ through Month 12 and were included in the FAS. GP-ELISA samples/results were missing or unevaluable for 13 subjects at Day 1 and 2 subjects at Months 1 and 12. PRNT samples/results were missing or unevaluable for 49 subjects at Day 1 and one subject at Month 12. Validated immunogenicity testing was not performed for subjects who received placebo.

ASaT population for safety analyses: All 1000 enrolled subjects were included in the ASaT population.

Compliance with safety follow up: In the V920 group, compliance with safety follow up was as follows: Week 1 (n= 495), Week 2 (n= 100), Month 1 (n= 491), Month 2 (n= 484), Month 4 (n= 479), Month 6 (n= 485), Month 8 (n= 481), Month 10 (n= 475), Month 12 (n= 486). In the placebo group, compliance with safety follow up was as follows: Week 1 (n= 498), Week 2 (n= 101), Month 1 (n= 494), Month 2 (n= 491), Month 4 (n= 489), Month 6 (n= 486), Month 8 (n= 484), Month 10 (n= 482), Month 12 (n= 487).

Protocol deviations: Protocol deviations included a subject who was pregnant at the time of administration of placebo and failure of 126 subjects to sign an informed consent addendum at a study close-out visit that described the final assessment and results of laboratory testing.

Reviewer comments: Compliance with safety follow up was 95% or higher at each study visit.

6.2.11 Immunogenicity Analyses

6.2.11.1 Analyses of Immunogenicity Endpoints

GP-ELISA
Baseline seropositivity (defined as ≥200 EU/mL by GP-ELISA) was observed in 97 (20.9%) of 464 subjects tested.

As this study was conducted during an ongoing Ebola outbreak, samples underwent gamma-irradiation to inactivate any possible Ebola virus prior to the performance of immunogenicity assays. The Applicant conducted a formal study was to evaluate the effect of gamma irradiation, at the target dose of 50 kilograys (kGy), on the serum

antibody titer (binding and neutralizing) collected from human subjects previously vaccinated with V920 (n= 60), the results of which were submitted as an amendment to the BLA. The effect of gamma irradiation on the reference standard was a 1.2-fold reduction in antibody titer. The effect of gamma irradiation on monoclonal antibodies spiked into antibody depleted human serum was a 2-fold decrease in ELISA concentration and PRNT titer.

The following table describes the GP-ELISA GMT, GMFR, and seroresponse rates by time point.

Table 17 GP-ELISA Geometric mean titer, geometric mean fold-rise, and seroresponse rates by time point

	GMT (n) [95% CI]	**GMFR (n) [95% CI]**	**2-Fold increase from baseline and >=200 EU/mL percent (m/n) [95% CI]**	**4-fold increase from baseline percent (m/n) [95% CI]**
At any time	-	-	93.8 (435/464) [91.1%, 95.8%]	82.3 (382/464) [78.5%, 85.7%]
Baseline	117.9 (464) [107.9, 128.7]	-	-	-
Month 1	994.7 (475) [915.0, 1,081.3]	8.5 (462) [7.7, 9.4]	90.0 (416/462) [86.9%, 92.6%]	76.8 (355/462) [72.7%, 80.6%]
Month 6	712.2 (477) [659.4, 769.3]	6.0 (464) [5.5, 6.6]	83.2 (386/464) [79.5%, 86.5%]	64.2 (298/464) [59.7%, 68.6%]
Month 12	661.4 (475) [613.2, 713.4]	5.6 (463) [5.1, 6.2]	80.1 (371/463) [76.2%, 83.7%	61.1 (283/463) [56.5%, 65.6%]

n = Number of subjects contributing to the analysis; CI = Confidence interval; GP-ELISA = Anti-Glycoprotein Human Enzyme-Linked Immunosorbent Assay (EU/mL); GMT = Geometric mean titer; GMFR: Geometric mean fold-rise

Source: Adapted from Original BLA 125690/1; V920-009 Immunogenicity Statistical Report, p. 21-27, Tables 4-5, 4-6, 4-7, and 4-8

Reviewer's comment: Humoral immune responses to V920 were observed, which peaked at Month 1 and, despite a decrease, remained 5.6-fold higher than baseline by Month 12. The clinical relevance of the values chosen to define seroresponse is unclear.

PRNT

Four (0.9%) of 428 subjects tested had a detectable PRNT at baseline, all of whom were also seropositive by GP-ELISA.

The following table describes the PRNT GMT, GMFR, and seroresponse rates by time point.

Table 18 PRNT Geometric mean titer, geometric mean fold-rise, and seroresponse rates by time point

	GMT (n) [95% CI]	**GMFR (n) [95% CI]**	**4-fold increase from baseline Percent (m/n) [95% CI]**
At any time	-	-	80.4 (344/428) [76.3%, 84.0%]
Baseline	< 35 (428) [<35, <35]	-	-
Month 1	116.8 (477) [106.0, 128.8]	6.5 (428) [5.9, 7.2]	69.2 (296/428) [64.5%, 73.5%]-
Month 6	76.8 (477) [69.9, 84.4]	4.4 (428) [4.0, 4.8]	55.1 (236/428) [50.3%, 59.9%]
Month 12	100.4 (476) [91.4, 110.3]	5.6 (427) [5.1, 6.2]	63.5 (271/427) [58.7%, 68.0%]

n = Number of subjects contributing to the analysis; CI = Confidence interval; GP-ELISA = Anti-Glycoprotein Human Enzyme-Linked Immunosorbent Assay (EU/mL); GMT = Geometric mean titer; GMFR: Geometric mean fold-rise
Source: Adapted from Original BLA 125690/1; V920-009 Immunogenicity Statistical Report, p. 30-34, Tables 4-9, 4-10, and 4-11.

Reviewer's comment: Similar to GP-ELISA titers, PRNT titers peaked at Month 1 and remained above baseline at Month 12 (GMFR of 5.6).

6.2.11.2 Analyses of Secondary Endpoints
Vaccine viremia
For the 24 subjects who participated in a sub-study to measure plasma levels of V920 RNA, RNA was detected in the plasma of two of eight subjects (25%) who had been assigned to receive V920 and in none of those who had been assigned to receive placebo. One subject had V920 RNA on Day 3 but not on Days 10 and 14, whereas the results in the second subject were positive on Days 3 and 10 but not on Day 14.

6.2.11.3 Subpopulation Analyses
Of the five subjects >65 years of age, four were included in the immunogenicity analysis. Of the 22 subjects with HIV, 20 were in included in the immunogenicity analysis.

The following table describes the GP-ELISA GMT and GMFR overall for the FAS and by subgroup (age, gender, baseline GP-ELISA, and HIV status).

Table 19 GP-ELISA Geometric mean titer and geometric mean fold-rise overall and by subgroup (age, gender, baseline GP-ELISA, and HIV status)

	Baseline GMT (n) [95% CI]	Month 1 GMT (n) [95% CI]	Month 1 GMFR (n) [95% CI]	Month 6 GMT (n) [95% CI]	Month 6 GMFR (n) [95% CI]	Month 12 GMT (n) [95% CI]	Month 12 GMFR (n) [95% CI]
Overall	117.9 (464) [107.9, 128.7]	994.7 (475) [915.0, 1,081.3]	8.5 (462) [7.7, 9.4]	712.2 (477) [659.4, 769.3]	6.0 (464) [5.5, 6.6]	661.4 (475) [613.2, 713.4]	5.6 (463) [5.1, 6.2]
18-50 years of age	120.7 (441) [110.3, 132.2]	1,000.7 (451) [917.9, 1,091.1]	8.3 (439) [7.5, 9.2]	708.3 (453) [654.1, 767.1]	5.8 (441) [5.3, 6.4]	653.7 (451) [604.7, 706.5]	5.4 (440) [4.9, 6.0]
>50 years of age	74.6 (23) [51.4, 108.2]	887.2 (24) [638.7, 1,232.4]	13.0 (23) [7.9, 21.2]	789.4 (24) [580.0, 1,074.4]	11.0 (23) [7.0, 17.3]	825.1 (24) [590.5, 1,152.7]	11.4 (23) [7.3, 17.7]
Female	87.6 (174) [75.1, 102.2]	1,112.6 (177) [964.9, 1,282.9]	12.7 (173) [10.7, 15.3]	871.3 (178) [756.7, 1,003.3]	10.0 (174) [8.5, 11.8]	818.2 (178) [710.3, 942.6]	9.4 (174) [7.9, 11.2]
Male	140.8 (290) [127.2, 156.0]	930.6 (298) [839.8, 1,031.3]	6.7 (289) [6.0, 7.4]	631.7 (299) [578.6, 689.5]	4.5 (290) [4.0, 4.9]	582.2 (297) [535.5, 633.0]	4.5 (290) [4.0, 4.9]
Baseline GP-ELISA ≥200 EU/mL	448.5 (97) [367.8, 546.9]	1,536.8 (95) [1,252.4, 1,885.9]	3.5 (95) [2.9, 4.2]	1,063.0 (97) [873.5, 1,293.6]	2.4 (97) [2.0, 2.8]	925.9 (97) [776.1, 1,104.6]	2.1 (97) [1.8, 2.4]
Baseline GP-ELISA <200 EU/mL	82.8 (367) [78.0, 87.8]	887.8 (367) [811.9, 970.7]	10.7 (367) [9.7, 11.9]	639.2 (367) [589.3, 693.3]	7.7 (367) [7.0, 8.5]	607.2 (366) [558.7, 659.8]	7.4 (366) [6.7, 8.1]
HIV positive	135.6 (17) [101.2, 181.9]	662.7 (20) [388.6, 1,129.9]	5.1 (17) [2.7, 9.4]	416.5 (20) [312.8, 554.7]	3.1 (17) [2.2, 4.5]	333.4 (20) [239.6, 463.9]	2.4 (17) [1.6, 3.8]

	Baseline GMT (n) [95% CI]	Month 1 GMT (n) [95% CI]	Month 1 GMFR (n) [95% CI]	Month 6 GMT (n) [95% CI]	Month 6 GMFR (n) [95% CI]	Month 12 GMT (n) [95% CI]	Month 12 GMFR (n) [95% CI]
HIV negative	117.2 (447) [107.0, 128.4]	1,012.6 (455) [930.9, 1,101.5]	8.7 (445) [7.9, 9.6]	729.1 (457) [673.8, 789.0]	6.2 (447) [5.6, 6.8]	681.6 (455) [631.3, 735.9]	5.8 (446) [5.3, 6.4]

n = Number of subjects contributing to the analysis; CI = Confidence interval; GP-ELISA = Anti-Glycoprotein Human Enzyme-Linked Immunosorbent Assay (EU/mL); GMT = Geometric mean titer; GMFR: Geometric mean fold-rise

Source: Adapted from Original BLA 125690/1; V920-009 Immunogenicity Statistical Report, p. 22-23, Tables 4-5 and 4-6

The following table describes the GP-ELISA seroresponse rates overall for the FAS and by subgroup (age, gender, baseline GP-ELISA, and HIV status).

Table 20 GP-ELISA seroresponse rates (2-fold increase from baseline and >=200 EU/mL and 4-fold increase from baseline) overall and by subgroup (age, gender, baseline GP-ELISA, and HIV status)

	2-Fold Increase from Baseline and >=200 EU/mL at any time Percent (m/n) [95% CI]	**4-Fold Increase from Baseline at any time Percent (m/n) [95% CI]**	**2-Fold Increase from Baseline and >=200 EU/mL Percent Month 1 (m/n) [95% CI]**	**4-Fold Increase from Baseline Month 1 Percent (m/n) [95% CI]**	**2-Fold Increase from Baseline and >=200 EU/mL Percent Month 6 (m/n) [95% CI]**	**4-Fold Increase from Baseline Month 6 Percent (m/n) [95% CI]**	**2-Fold Increase from Baseline and >=200 EU/mL Month 12 Percent (m/n) [95% CI]**	**4-Fold Increase from Baseline Month 12 Percent (m/n) [95% CI]**
Overall	93.8 (435/464) [91.1%, 95.8%]	82.3 (382/464) [78.5%, 85.7%]	90.0 (416/462) [86.9%, 92.6%]	76.8 (355/462) [72.7%, 80.6%]	83.2 (386/464) [79.5%, 86.5%]	64.2 (298/464) [59.7%, 68.6%]	80.1 (371/463) [76.2%, 83.7%]	61.1 (283/463) [56.5%, 65.6%]
18-50 years of age	93.4 (412/441) [90.7%, 95.6%]	81.9 (361/441) [77.9%, 85.3%]	89.5 (393/439) [86.3%, 92.2%]	76.3 (335/439) [72.0%, 80.2%]	82.8 (365/441) [78.9%, 86.2%]	63.5 (280/441) [58.8%, 68.0%]	79.3 (349/440) [75.2%, 83.0%]	59.8 (263/440) [55.0%, 64.4%]
>50 years of age	100.0 (23/23) [85.2%, 100%]	91.3 (21/23) [72.0%, 98.9%]	100.0 (23/23) [85.2%, 100%]	87.0 (20/23) [66.4%, 97.2%]	91.3 (21/23) [72.0%, 98.9%]	78.3 (18/23) [56.3%, 92.5%]	95.7 (22/23) [78.1%, 99.9%]	87.0 (20/23) [66.4%, 97.2%]
Female	94.3 (164/174) [89.7%, 97.2%]	90.2 (157/174) [84.8%, 94.2%]	90.8 (157/173) [85.4%, 94.6%]	84.4 (146/173) [78.1%, 89.5%]	89.7 (156/174) [84.1%, 93.8%]	82.2 (143/174) [75.7%, 87.6%]	86.2 (150/174) [80.2%, 91.0%]	77.6 (135/174) [70.7%, 83.5%]
Male	93.4 (271/290) [90.0%, 96.0%]	77.6 (225/290) [72.3%, 82.3%]	89.6 (259/289) [85.5%, 92.9%]	72.3 (209/289) [66.8%, 77.4%]	79.3 (230/290) [74.2%, 83.8%]	53.4 (155/290) [47.5%, 59.3%]	76.5 (221/289) [71.1%, 81.2%]	51.2 (148/289) [45.3%, 57.1%]
Baseline GP-ELISA ≥200 EU/mL	81.4 (79/97) [72.3%, 88.6%]	46.4 (45/97) [36.2%, 56.8%]	75.8 (72/95) [65.9%, 84.0%]	35.8 (34/95) [26.2%, 46.3%]	55.7 (54/97) [45.2%, 65.8%]	22.7 (22/97) [14.8%, 32.3%]	48.5 (47/97) [38.2%, 58.8%]	18.6 (18/97) [11.4%, 27.7%]
Baseline GP-ELISA <200 EU/mL	97.0 (356/367) [94.7%, 98.5%]	91.8 (337/367) [88.5%, 94.4%]	93.7 (344/367) [90.7%, 96.0%]	87.5 (321/367) [83.6%, 90.7%]	90.5 (332/367) [87.0%, 93.3%]	75.2 (276/367) [70.5%, 79.5%]	88.5 (324/366) [84.8%, 91.6%]	72.4 (265/366) [67.5%, 76.9%]
HIV positive	76.5 (13/17) [50.1%, 93.2%]	64.7 (11/17) [38.3%, 85.8%]	70.6 (12/17) [44.0%, 89.7%]	64.7 (11/17) [38.3%, 85.8%]	76.5 (13/17) [50.1%, 93.2%]	29.4 (5/17) [10.3%, 56.0%]	52.9 (9/17) [27.8%, 77.0%]	17.6 (3/17) [3.8%, 43.4%]

	2-Fold Increase from Baseline and >=200 EU/mL at any time Percent (m/n) [95% CI]	4-Fold Increase from Baseline at any time Percent (m/n) [95% CI]	2-Fold Increase from Baseline and >=200 EU/mL Percent Month 1 (m/n) [95% CI]	4-Fold Increase from Baseline Month 1 Percent (m/n) [95% CI]	2-Fold Increase from Baseline and >=200 EU/mL Percent Month 6 (m/n) [95% CI]	4-Fold Increase from Baseline Month 6 Percent (m/n) [95% CI]	2-Fold Increase from Baseline and >=200 EU/mL Month 12 Percent (m/n) [95% CI]	4-Fold Increase from Baseline Month 12 Percent (m/n) [95% CI]
HIV negative	94.4 (422/447) [91.9%, 96.3%]	83.0 (371/447) [79.2%, 86.4%]	90.8 (404/445) [87.7%, 93.3%]	77.3 (344/445) [73.1%, 81.1%]	83.4 (373/447) [79.7%, 86.8%]	65.5 (293/447) [60.9%, 69.9%]	81.2 (362/446) [77.2%, 84.7%]	62.8 (280/446) [58.1%, 67.3%]

n = number of subjects contributing to the analysis; m = number of subjects seropositive; CI = Confidence interval; GP-ELISA = Anti-Glycoprotein Human Enzyme-Linked Immunosorbent Assay (EU/mL); GMT = Geometric mean titer; GMFR: Geometric mean fold-rise
Source: Adapted from Original BLA 125690/1; V920-009 Immunogenicity Statistical Report, p. 25-27, Tables 4-7 and 4-8

Reviewer's comment: The Month 1 GP-ELISA GMT was higher for subjects 18 to 50 years of age compared to subjects ≥50; however, at all subsequent time points, the GMT was higher for subjects >50 years of age. The GMFR and seroresponse rates were higher in the older subjects at every post-vaccination time point, suggesting that subjects ≥50 years of age are capable of mounting a robust humoral response to vaccination with V920. Females had consistently higher GMTs, GMFRs, and seroresponse rates than males.

It is unclear whether the high rate of baseline seropositivity (20.9% of subjects) reflects assay variability or previous exposure to wild-type Ebola or a related virus. The lack of a robust anamnestic response to V920 in baseline seropositive subjects (at Month 1, GP-ELISA GMFR was 3.5 and seroconversion rate was 46.4%) suggests either that the high rate of baseline seropositivity is due to assay variability or that V920 does not elicit a strong anamnestic response following wild-type Ebola exposure. Further, while the GMTs are higher at every time point for baseline seropositive subjects, the GMFR and seroresponse rates are lower compared to baseline seronegatives. It is unclear whether the muted responses relative to baseline in the seropositive subgroup is an artifact of the assay or interference from pre-existing antibodies.

HIV positive subjects had lower GMTs, GMFRs, and seroresponse rates compared to HIV negative subjects; however, the GMFR at the Month 1 time point was 5.1, indicating that humoral immune responses to V920 can be achieved in this group.

PRNT
Four (0.9%) of 428 subjects tested had a detectable PRNT at baseline, all of whom were also seropositive by GP-ELISA.

The following table describes the PRNT GMT and GMFR overall for the FAS and by subgroup (age, gender, baseline GP-ELISA, and HIV status).

Table 21 PRNT Geometric mean titer and geometric mean fold-rise overall and by subgroup (age, gender, baseline GP-ELISA, and HIV status)

	Baseline GMT (n) [95% CI]	Month 1 GMT (n) [95% CI]	Month 1 GMFR (n) [95% CI]	Month 6 GMT (n) [95% CI]	Month 6 GMFR (n) [95% CI]	Month 12 GMT (n) [95% CI]	Month 12 GMFR (n) [95% CI]
Overall	< 35 (428) [<35, <35]	116.8 (477) [106.0, 128.8]	6.5 (428) [5.9, 7.2]	76.8 (477) [69.9, 84.4]	4.4 (428) [4.0, 4.8]	100.4 (476) [91.4, 110.3]	5.6 (427) [5.1, 6.2]
18-50 years of age	< 35 (404) [<35, <35]	114.5 (453) [103.7, 126.3]	6.3 (404) [5.7, 7.0]	74.6 (453) [67.8, 82.2]	4.2 (404) [3.9, 4.7]	98.7 (452) [89.6, 108.7]	5.5 (403) [5.0, 6.1]
>50 years of age	< 35 (24) [<35, <35]	171.7 (24) [98.3, 299.9]	9.8 (24) [5.6, 17.1]	132.2 (24) [83.6, 209.0]	7.6 (24) [4.8, 11.9]	138.8 (24) [92.5, 208.1]	7.9 (24) [5.3, 11.9]
Female	< 35 (157) [<35, <35]	157.7 (178) [134.6, 184.7]	8.6 (157) [7.3, 10.2]	119.5 (178) [101.2, 141.2]	7.0 (157) [6.0, 8.2]	158.9 (178) [135.6, 186.2]	9.0 (157) [7.7, 10.6]
Male	< 35 (271) [<35, <35]	97.7 (299) [86.7, 110.2]	5.5 (271) [4.9, 6.2]	59.0 (299) [53.3, 65.5]	3.3 (271) [3.0, 3.7]	76.3 (298) [68.7, 84.7]	4.2 (270) [3.8, 4.7]
Baseline GP-ELISA ≥200 EU/mL	< 35 (82) [<35, <35]	119.9 (97) [92.3, 155.7	5.6 (82) [4.4, 7.2]	72.2 (97) [55.1, 94.5]	3.6 (82) [2.8, 4.6]	99.4 (97) [77.2, 127.9]	4.7 (82) [3.6, 6.0]
Baseline GP-ELISA <200 EU/mL	< 35 (334) [<35, <35]	116.5 (367) [105.1, 129.2]	6.8 (334) [6.1, 7.5]	79.7 (367) [72.2, 87.9]	4.7 (334) [4.2, 5.2]	102.2 (366) [92.3, 113.0]	5.9 (333) [5.3, 6.6]
HIV positive	< 35 (14) [<35, <35]	85.2 (20) [48.2, 150.6]	4.9 (14) [2.6, 9.0]	< 35 (20) [<35, 50.5]	2.3 (14) [1.3, 4.1]	38.5 (20) [<35, 59.0]	2.4 (14) [1.4, 4.2]
HIV negative	< 35 (414) [<35, <35]	118.5 (457) [107.3, 130.8]	6.6 (414) [5.9, 7.3]	79.7 (457) [72.4, 87.7]	4.5 (414) [4.1, 4.9]	104.7 (456) [95.2, 115.1]	5.8 (413) [5.2, 6.3]

n = number of subjects contributing to the analysis; CI = Confidence interval; PRNT = Plaque reduction neutralization test; GMT = Geometric mean titer; GMFR: Geometric mean fold-rise

Source: Adapted from Original BLA 125690/1; V920-009 Immunogenicity Statistical Report, p. 30-32, Tables 4-9 and 4-10

Table 22 PRNT seroresponse rates (4-fold increase from baseline) overall and by subgroup (age, gender, baseline GP-ELISA, and HIV status)

	At any time Percent (m/n) [95% CI]	**Month 1 Percent (m/n) [95% CI]**	**Month 6 Percent (m/n) [95% CI]**	**Month 12 Percent (m/n) [95% CI]**
Overall	80.4 (344/428) [76.3%, 84.0%]	69.2 (296/428) [64.5%, 73.5%]	55.1 (236/428) [50.3%, 59.9%]	63.5 (271/427) [58.7%, 68.0%]
18-50 years of age	79.7 (322/404) [75.4%, 83.5%]	68.6 (277/404) [63.8%, 73.1%]	54.2 (219/404) [49.2%, 59.1%]	62.8 (253/403) [57.9%, 67.5%]
>50 years of age	91.7 (22/24) [73.0%, 99.0%]	79.2 (19/24) [57.8%, 92.9%]	70.8 (17/24) [48.9%, 87.4%]	75.0 (18/24) [53.3%, 90.2%]
Female	89.8 (141/157) [84.0%, 94.1%]	77.7 (122/157) [70.4%, 84.0%]	75.2 (118/157) [67.6%, 81.7%]	79.6 (125/157) [72.5%, 85.6%]
Male	74.9 (203/271) [69.3%, 80.0%]	64.2 (174/271) [58.2%, 69.9%]	43.5 (118/271) [37.6%, 49.7%]	54.1 (146/270) [47.9%, 60.1%]
Baseline GP-ELISA ≥200 EU/mL	72.0 (59/82) [60.9%, 81.3%]	63.4 (52/82) [52.0%, 73.8%]	47.6 (39/82) [36.4%, 58.9%]	52.4 (43/82) [41.1%, 63.6%]
Baseline GP-ELISA <200 EU/mL	83.2 (278/334) [78.8%, 87.1%]	71.0 (237/334) [65.8%, 75.8%]	58.1 (194/334) [52.6%, 63.4%]	67.3 (224/333) [61.9%, 72.3%]
HIV positive	71.4 (10/14) [41.9%, 91.6%]	57.1 (8/14) [28.9%, 82.3%]	28.6 (4/14) [8.4%, 58.1%]	35.7 (5/14) [12.8%, 64.9%]
HIV negative	80.7 (334/414) [76.5%, 84.4%]	69.6 (288/414) [64.9%, 74.0%]	56.0 (232/414) [51.1%, 60.9%]	64.4 (266/413) [59.6%, 69.0%]

n = number of subjects contributing to the analysis; m = number of subjects seropositive; CI = Confidence interval; PRNT = Plaque reduction neutralization test

Source: Adapted from Original BLA 125690/1; V920-009 Immunogenicity Statistical Report, p. 34, Tables 4-11

Reviewer's comment: The pattern of PRNT responses in each subgroup was generally similar to those seen for GP-ELISA responses, with a higher magnitude of response observed in subjects ≥50 years of age, females, and HIV negative subjects. However, the impact of baseline GP-ELISA seropositivity on PRNT responses was less marked than the impact on GP-ELISA titers; the impact of baseline seropositivity on functional antibody response to V920 remains unclear.

6.2.11.4 Dropouts and/or Discontinuations
See Section 6.2.10.1.3 (Subject disposition) for information on dropouts and discontinuations.

6.2.12 Safety Analyses

6.2.12.1 Methods

All safety analyses were conducted using the ASaT population (i.e., all 500 subjects enrolled in each group). Solicited local (pain and local reaction [erythema, swelling, blistering, ulceration/necrosis]) and systemic (body temperature, weight, joint problems [pain/tenderness, swelling, stiffness, redness/warmth], or targeted symptoms [feverishness, fatigue, muscle pain, headache, nausea, abnormal sweating, rash, mouth ulcers, unexplained bleeding or bruising, joint pain, or "other" symptoms]) adverse events were collected at 30 minutes, 1 week, and 1 month following vaccination. Joint events were solicited at a Week 2 visit for a subset of subjects (n= 200).

A total of 22 subjects (4.4%) in the V920 group and 31 subjects (6.2%) in the placebo group were HIV-positive. A sub-analysis of safety events was performed for the cohort of subjects who were HIV-positive.

Reviewer's comment: HIV testing was conducted as part of screening procedures and identified some subjects with previously unreported HIV.

6.2.12.2 Overview of Adverse Events

The following table provides an overview of adverse events for the 12-month period following vaccination.

Table 23 Summary of adverse events (subjects with visit in the Day 1 to Year 1 time period)

Subjects in population with follow-up:	**V920 (N= 500) n (%)**	**Placebo (N= 500) n (%)**	**Total (N= 500) n (%)**
With 1 or more AEs	360 (72.0)	283 (56.6)	643 (64.3)
With injection-site AEs	170 (34.0)	56 (11.2)	226 (22.6)
With SAEs	47 (9.4)	59 (11.8)	106 (10.6)
Who died	5 (1.0)	6 (1.2)	11 (1.1)

AE= adverse event; SAE= serious adverse event
Source: Adapted from Original BLA 125690/1; Clinical Study Report V920-009, p.58, Table 12-1

Solicited local adverse events

Injection site pain was the most commonly reported local event in the 1-month period following vaccination and was reported more frequently after V920 (34.0% of subjects) compared to placebo (11.2%). Most events of injection site pain were reported at the Week 1 visit. At the Month 1 visit, reports of injection site pain were comparable between the V920 (1.6% of subjects) and placebo (1.0% of subjects) groups.

Local reactions (erythema, swelling, blistering, or ulceration/necrosis) were reported by 1.8% of subjects after V920 and 0.8% of subjects after placebo. All local events were mild to moderate; the proportion of subjects reporting any moderate local event was higher after V920 (4.1% of subjects) compared to placebo (1.8% of subjects).

HIV-infected subjects
Injection site pain was the most commonly reported local event in the 1-month period following vaccination and was reported more frequently after V920 (31.8% of subjects) compared to placebo (12.9%). By Month 1, no HIV-infected subjects reported injection site reactions.

Local reactions were reported by 13.6% of HIV-infected subjects after V920 and no subjects after placebo. All local events were mild to moderate; moderate events were only reported after V920, including two subjects with moderate events of local reaction.

Reviewer's comment: The proportion of subjects in each treatment group reporting injection site reactions was comparable between HIV-infected subjects and all subjects.

Solicited systemic adverse events
Any solicited local event was reported by 61.6% of subjects in the V920 group compared to 43.3% of subjects in the placebo group in the 1-month period following vaccination. The following tables describe the proportion of subjects reporting solicited systemic events overall in the 1-month period following vaccination and at the Week 1 visit (the time point at which the differences between the groups were greatest).

Table 24 Subjects with solicited systemic adverse events (including the Week 1, Week 2 [subset of ~200 subjects], and Month 1 visit):

MedDRA Preferred Term	V920 N= 498 n (%)	Placebo N= 499 n (%)
Headache	184 (36.9)	116 (23.2)
Pyrexia	171 (34.3)	74 (14.8)
Myalgia	162 (32.5)	114 (22.8)
Fatigue	92 (18.5)	67 (13.4)
Arthralgia	35 (7.0)	29 (5.8)
Nausea	40 (8.0)	22 (4.4)
Rash	18 (3.6)	16 (3.2)
Hyperhidrosis	16 (3.2)	13 (2.6)
Mouth ulceration	13 (2.6)	13 (2.6)
Joint swelling	2 (0.4)	2 (0.4)
Arthropathy	3 (0.6)	1 (0.2)
Joint stiffness	2 (0.4)	1 (0.2)
Hemorrhage	1 (0.2)	0 (0)

Source: Adapted from Original BLA 125690/1; Clinical Study Report V920-009, p.64, Table 12-6

Table 25 Subjects with solicited systemic adverse events (Week 1 visit):

MedDRA Preferred Term	V920 N= 495 n (%)	Placebo N= 498 n (%)
Headache	158 (31.9)	84 (16.9)
Pyrexia	151 (30.5)	45 (9.0)
Myalgia	133 (26.9)	66 (13.3)
Fatigue	76 (15.4)	44 (8.8)
Arthralgia	25 (5.1)	17 (3.4)
Nausea	30 (6.1)	15 (3.0)
Hyperhidrosis	14 (2.8)	8 (1.6)
Mouth ulceration	8 (1.6)	6 (1.2)
Rash	6 (1.2)	7 (1.4)
Arthropathy	3 (0.6)	1 (0.2)
Joint swelling	1 (0.2)	0 (0)

Source: Adapted from Original BLA 125690/1; Clinical Study Report V920-009, p.111, Table 14.3-5

Any solicited local event was reported by 56.4% of subjects in the V920 group compared to 30.5% of subjects in the placebo group in the 1 week period following vaccination; however, at the Month 1 visit, the proportion of subjects with 1 or more solicited systemic adverse events was comparable after V920 (26.1%) compared to placebo (25.7%) and the proportions of subjects with each individual event were generally comparable.

Temperatures were obtained only at the Week 1 and Month 1 visits. A maximum temperature of ≥38.0 °C (100.4 °F) was reported by 0.2% of subjects in the V920 group and 0.4% of subjects in the placebo group. No subject had a maximum temperature of ≥39.0 °C.

One subject in the V920 group reported moderate events of fatigue, headache, myalgia, and pyrexia; the remaining solicited systemic events were mild.

Reviewer's comment: Fatigue, pyrexia, and myalgia were the most commonly reported solicited events in both the V920 and placebo groups but were more frequently reported after V920. Temperature measurements were obtained only at Week 1 and Month 1 and thus are unlikely representative of the true incidence of fever, which would be expected to occur within the first week after vaccination; pyrexia was commonly reported in the week following vaccination with V920 (30.5% of subjects).

Data on duration and outcome of solicited events, including joint symptoms, was not collected. While it appears from the Month 1 visit data that fewer subjects were reporting solicited symptoms, the mean and median duration of specific events is not elucidated from the data provided.

HIV-infected subjects
In the 1-month period following vaccination, the proportion of HIV-infected subjects reporting solicited systemic events was higher in the V920 group (63.6% of subjects) compared to the placebo group (54.8% of subjects). The proportions of subjects reporting solicited systemic events was comparable between subjects with HIV (63.6% V920, 54.8% placebo) and without HIV (61.6% V920, 42.5% placebo). Solicited systemic events were reported more frequently at the Week 1 visit compared to the Month 1 visit.

At the Month 1 visit, the proportions of HIV-infected subjects reporting solicited systemic events was comparable between the V920 and placebo groups.

The most frequently reported solicited systemic events in HIV-infected and uninfected subjects included myalgia, headache, pyrexia, and fatigue. Regardless of treatment assignment, these events were reported by a higher proportion of subjects who were HIV-infected compared to HIV-uninfected subjects:

- HIV-positive: myalgia (40.9% V920, 29.0% placebo), headache (31.8% V920, 29.0% placebo), pyrexia (31.8% V920, 25.8% placebo), and fatigue (22.7% V920, 19.4% placebo).
- HIV-negative: myalgia (32.1% V920, 22.4% placebo), headache (37.2% V920, 22.9% placebo), pyrexia (34.5% V920, 14.1% placebo), and fatigue (18.3% V920, 13.0% placebo).

All solicited systemic events reported by subjects with HIV were mild.

Reviewer's comment: The pattern of solicited systemic events reported by subjects infected with HIV was comparable to that observed in HIV-negative subjects.

Unsolicited adverse events

Unsolicited adverse events were collected at the Week 1 and Month 1 visits. In the Day 1- Week 1 time period, unsolicited adverse events were reported by 12.4% of subjects in the V920 group and 8.6% of subjects in the placebo group. Unsolicited events reported by more than 1 subject and by a higher proportion of subjects in the V920 group compared to placebo include: constipation (0.6% of subjects after V920 and 0.2% of subjects after placebo), diarrhea (1.0% of subjects after V920 and 0.8% of subjects after placebo), chills (1.0% of subjects after V920 and 0.8% of subjects after placebo), pain (0.4% of subjects after V920 and 0% of subjects after placebo), decreased appetite (2.4% of subjects after V920 and 1.4% of subjects after placebo), increased appetite (0.6% of subjects after V920 and 0.4% of subjects after placebo), dizziness (1.2% of subjects after V920 and 0.6% of subjects after placebo), and cough (1.0% of subjects after V920 and 0.6% of subjects after placebo).

Reviewer's comments: In the BLA, the Applicant provided a publication describing V920-009 (Kennedy, Stephen B., et al. "Phase 2 placebo-controlled trial of two vaccines to prevent Ebola in Liberia." New England Journal of Medicine 377.15 (2017): 1438-1447). Minor discrepancies between Supplemental Table S6 of this publication and the ADAE dataset for Study 009 with regard to unsolicited adverse events occurring between Day 1 and Week 1 were noted. In response to an IR regarding these discrepancies, the Applicant acknowledged that the process of migrating and mapping data from the Sponsor may have resulted in minor discrepancies between the manuscript tables and the ADAE dataset due to coding. The Applicant asserts that these small discrepancies do not impact the overall interpretation or conclusions for the safety data; as the overall occurrence of events was low and the identified discrepancies were minor, this was deemed acceptable.

In the Month 1 time period, unsolicited adverse events were reported by 18.2% of subjects in the V920 group and 15.2% of subjects in the placebo group. Unsolicited events reported by more than one subject and by a higher proportion of subjects in the V920 group compared to placebo include: abdominal pain lower (0.4% of subjects after V920 and 0% of subjects after placebo), constipation (0.6% of subjects after V920 and

0.2% of subjects after placebo), diarrhea (1.6% of subjects after V920 and 1.2% of subjects after placebo), vomiting (0.4% of subjects after V920 and 0% of subjects after placebo), asthenia (0.4% of subjects after V920 and 0.2% of subjects after placebo), chest pain (0.8% of subjects after V920 and 0.4% of subjects after placebo), pain (0.4% of subjects after V920 and 0.2% of subjects after placebo), decreased appetite (3.8% of subjects after V920 and 2.4% of subjects after placebo), back pain (0.8% of subjects after V920 and 0% of subjects after placebo), dizziness (1.4% of subjects after V920 and 0.6% of subjects after placebo), and rhinorrhea (0.8% of subjects after V920 and 0.4% of subjects after placebo).

Reviewer comments: Data for unsolicited events reported at the Week 1 and through Month 1 visits were provided as a response to an IR (Amendment 31). Unsolicited adverse events were not evaluated for relatedness. In general, the rates of each unsolicited event were comparable, and of the events occurring more frequently after V920 than placebo, the maximum relative difference was 1.4% (decreased appetite). There was no pattern of events to suggest a specific safety concern.

6.2.12.3 Deaths

In the Month 1 time period, a fatal event of *Pneumocystis jirovecii* pneumonia was reported by a subject in the placebo group.

In the Year 1 time period, fatal events were reported by five subjects in the V920 group and six subjects in the placebo group. None of the deaths were considered related to the study vaccine by the Investigator.

In the V920 group, the following fatal SAEs were reported:

- A 56-year old male with no medical history died due to an unknown cause 80 days after V920. He reported an event of syncope while on the toilet 2 days prior to his death. He was seen by a physician who provided an “injection” and oral medication for cough. The subject was walking to a shop when he fell and died suddenly. On an unknown date, the subject had an elevated D-dimer (baseline= 9.8 and “1 month” 10.33 [units not provided]). Information on concomitant medication was not provided.
- A 42-year old male with no medical history died from an unknown cause 273 days after V920. According to a family member, the subject was ill during the Christmas holiday and was subsequently found unresponsive at home. Information on concomitant medication was not provided.

Reviewer’s comment: There is limited information available for the fatal events due to unknown causes which precludes a full assessment of causality; however, there is no clear temporal relationship to vaccination and death due to an unknown cause was similarly reported by a subject in the placebo group.

- A 24-year old male with no medical history (HIV negative) reported an SAE of pulmonary tuberculosis 233 days after V920. Approximately 1 month later, the subject died of pulmonary tuberculosis. Information on concomitant medication was not provided.
- A 35-year old female with a history of HIV/AIDS reported SAEs of gastroenteritis (37 days after V920) and respiratory failure (41 days after V920). Prior to the

diagnosis of gastroenteritis, the subject reported events of fever, bloody diarrhea, oral candidiasis, and pelvic inflammatory disease. At the time of onset of the SAE of gastroenteritis, she had not received antiretrovirals for 2 years and her CD4 count was "76 mm." She was started on antiretrovirals and hospitalized with diarrhea and vomiting. She was discharged home after three days and then was readmitted after an event of respiratory failure (no further details available) the day following discharge from the hospital. On day 42 after V920 she was readmitted to the hospital with diarrhea. While hospitalized, she was reported to have an event of respiratory failure and died 47 days after V920.

- A 74-year old male with no reported medical history was reported to have an event of malignant hypertension 218 days after V920 and died the same day. Approximately 4 months prior to the fatal event, the subject was seen in an acute care clinic and was noted to have elevated blood pressure of 160/110 (units not reported), for which he was prescribed hydrochlorothiazide. In the month prior to his death, he was again seen in clinic with a history of a fall, at which time his blood pressure was 110/80 (units not reported). On the day of his death, he suddenly fell ill and was noted to have a blood pressure of 200/120 (units not reported). Information on concomitant medication was not provided.

Reviewer's comment: Initially, the Applicant provided narratives for the deaths that were limited in scope and content. In response to an IR, the Applicant provided Council for International Organizations of Medical Sciences (CIOMS) reports for all SAEs and the CIOMS reports for all serious and fatal events in Amendment 31 to the BLA, which were reviewed. Other than the deaths due to an unknown cause, a plausible alternative etiology is provided for the remaining fatalities (infectious, complications of AIDS, and malignant hypertension leading to death). The causality assessment provided by the Investigator appears appropriate for the fatal SAEs. The fatal events occurring after V920 all had a time to onset of >30 days and there is no clear pattern of events or biologically plausible mechanism to suggest causality from the available information.

In the placebo group, the following fatal SAEs were reported:

- A 52-year old female with no medical history reported an SAE of severe, recurrent headache 317 days after placebo. The subject died due to multiple organ dysfunction syndrome 331 days after placebo. Information on concomitant medication was not provided.
- A 47-year old female with no medical history died due to unknown cause 316 days after placebo. Information on concomitant medication was not provided.
- A 27-year old female with a history of HIV infection reported SAEs of pulmonary tuberculosis (113 days after placebo) and malaria (142 days after placebo). The subject died due to pulmonary tuberculosis 181 days after placebo.
- A 28-year old male with no medical history (HIV negative) reported SAEs of malaria (12 days after placebo) and pulmonary tuberculosis (244 days after placebo). The subject died due to pulmonary tuberculosis 338 days after placebo. Information on concomitant medication was not provided.
- A 30-year old male with no medical history reported an SAEs of renal failure (34 days after placebo) and malignant hypertension (43 days after placebo). The subject died 60 days after placebo due to renal failure. The subject had a creatinine of 14 mg/dL (normal range: 0.6-1.3 mg/dL) on Day 1 and a creatinine of 10.7 mg/dL at the Week 1 visit. Information on concomitant medication was not provided.

- An 18-year old female with a history of HIV infection died due to *Pneumocystis jirovecii* pneumonia 22 days after placebo.

HIV-infected subjects
Overall, a higher proportion of HIV-positive subjects (5.7%) reported an AE resulting in death compared to HIV-negative subjects (0.8%) and of the 12 total fatalities, three (25%) occurred in subjects with HIV-infection as described above, including two in the V920 group and one in the placebo group.

Reviewer's comment: The overrepresentation of HIV-positive subjects in the total fatalities was observed in both the V920 and placebo groups and likely reflects the natural history of the disease. The lack of information on the clinical status (e.g., CD4 count, drug regimens, viral load) of HIV-infected subjects precludes a full assessment of the impact of V920 vaccination on the trajectory of HIV-related diseases.

6.2.12.4 Nonfatal Serious Adverse Events

In the Month 1 period, nonfatal SAEs were reported by six subjects in the V920 group (1.2%) and nine subjects in the placebo group (1.8%), with two related SAEs reported in each group. The six nonfatal SAEs in the V920 group were all malaria. Of the nine nonfatal SAEs in the placebo group, eight were events of malaria and one was an event of vaginal hemorrhage. Causality for two events of malaria in the V920 group and one event of malaria and one event of vaginal hemorrhage in the placebo group was assessed as related to study vaccine/placebo by the investigator in the CRFs; however, the medical officer assessed the causality for these events as not related to study vaccine/placebo.

In the Year 1 time period, nonfatal SAEs were reported by 42 subjects in the V920 group (8.4%) and 53 subjects in the placebo group (10.6%). Malaria was the most commonly reported SAE in both treatment groups and was more commonly reported after placebo than V920.

Reviewer's comment: In review of the narratives for malaria events, many events were considered serious due to meeting the criterion of medically significant. It is possible that some reports of malaria that were closely temporally related to administration of V920 reflect symptoms attributable to vaccination (e.g., fever, myalgias, joint pain) in the setting of asymptomatic parasitemia in a region where malaria is endemic.

The following table summarizes all non-fatal SAEs that occurred in a higher proportion of subjects in the V920 group compared to the placebo group:

Table 26 Non-fatal SAEs that occurred in a higher proportion of subjects in the V920 group compared to the placebo group in the Day 1 to Year 1 time period

MedDRA Preferred Term	**V920 n (%) N=500**	**Placebo n (%) N=500**
Postpartum hemorrhage	1 (0.2)	0 (0)
Cerebrovascular accident	2 (0.4)	0 (0)
Fetal death	2 (0.4)	0 (0)
Gastroenteritis	3 (0.6)	0 (0)

MedDRA Preferred Term	V920 n (%) N=500	Placebo n (%) N=500
Depression	1 (0.2)	0 (0)
Hepatic cirrhosis	1 (0.2)	0 (0)
Botulism	1 (0.2)	0 (0)
Typhoid fever	1 (0.2)	0 (0)

Source: Original BLA 125690/2; V920-009 ADAE dataset

The available information on the SAEs reported after V920 in Table 26 is as follows:

- Hepatic cirrhosis was reported by a 32-year old male with a history of chronic Hepatitis B infection 234 days after V920. He presented with symptoms of scleral icterus, fever, nausea, chills, headache, poor appetite, body pain, and dysuria. He was diagnosed with a urinary tract infection and malaria and treated for these conditions. At that time, liver function tests were abnormal, including an elevated direct bilirubin. Lamivudine was provided to the subject.
- Botulism was reported by a 30-year old male 96 days after V920. The subject presented with abdominal pain, fever, nausea, joint and body pain, cough, vomiting, diarrhea, and productive cough. He was hospitalized and treated with antibiotics and antitoxin, although the diagnosis of botulism was not based on any laboratory testing.
- Gastroenteritis was reported by a 32- year old male 110 days after V920, a 22 - year old male 203 days after V920, and a 35-year old female 37 days after V920. No diagnostic testing was provided for these three reports.
- Typhoid fever was reported by an 18-year old female 105 days after V920. The subject presented with body pain. A Widal antigen test was positive and she was diagnosed with typhoid fever and treated as an outpatient with ciprofloxacin.
- Cerebrovascular accidents were reported by two subjects.
    - A 47-year old female reported symptoms of confusion, left sided hemiplegia, slurred speech, and left facial droop after a fall at home 128 days after V920. In the emergency room, her blood pressure was 200/130. She had no reported previous history of hypertension and concomitant mediations were not reported. She was treated with antihypertensives and aspirin and was able to ambulate without assistance in follow up.
    - A 61-year old female with a history of hypertension reported an acute stroke 334 days after V920. Concomitant medications included atenolol and hydrochlorothiazide, with which she was not compliant. She presented with symptoms of left arm and leg weakness and slurred speech. The blood pressure was 210/110 in the hospital and she was admitted and treated with hydralgine and hydrochlorothiazide.
- Fetal deaths were reported by two subjects.
    - A 20-year old woman became pregnant at an unknown time and went into labor 330 days after V920, at which time she was considered to be full term. She delivered a stillborn infant at home and subsequently reported postpartum hemorrhage resulting in anemia (hemoglobin 6.0 mg/dL) and hypovolemic shock requiring hospitalization.
    - A 27-year old woman became pregnant with a last menstrual period approximately 1 month after V920. At 22 weeks gestation and 199 days after V920, the subject presented with no fetal movement. A diagnosis of intrauterine fetal demise was made by ultrasound. A malaria smear was

positive. The subject was induced and all products of conception were expelled.

- Depression was reported by a 67-year old female 51 days after V920 with a concurrent diagnosis of neurosyphilis and multiple social stressors.

Reviewer's comment: Most non-fatal SAEs had likely infectious etiologies and were temporally distant from vaccination. The two reports of cerebrovascular accidents were temporally distant from vaccination and were associated with hypertension, which was a likely contributing factor. The reports of cardiovascular accident are discussed in additional detail in Section 8.4.8. The full-term stillborn infant was born at home, and confounding factors that may have resulted in the loss are not provided in the SAE report, such as the presence of birth defects or a nuchal cord. The intrauterine fetal demise was confounded by a concurrent diagnosis of malaria, a known risk factor for poor outcomes in pregnancy. The causality assessment provided by the Investigator appears appropriate for these non-fatal SAEs. Non-fatal SAEs occurring after V920 all had a time to onset of >30 days after vaccination and there is no clear pattern of events or biologically plausible mechanism to suggest causality from the available information.

HIV-infected subjects
In the Year 1 time period, nonfatal SAEs were reported by one HIV-infected subject (non-fatal SAE of gastroenteritis and fatal SAE of respiratory failure) in the V920 group and six HIV-infected subjects (five non-fatal events of malaria and one fatal event each of *Pneumocystis jirovecii* pneumonia and pulmonary tuberculosis) in the placebo group.

Pregnancy
Subjects who reported being pregnant in the first 30 days after vaccination were followed for the outcome of their pregnancies. Four subjects reported SAEs classified in the pregnancy, puerperium and perinatal conditions SOC, including events of fetal death and postpartum hemorrhage in the V920 group and events of abortion incomplete and abortion spontaneous in the placebo group.

In addition, three pregnancies resulting in live births were reported by subjects in the placebo group.
An additional subject in the placebo group was discovered to have been pregnant at the time of vaccination, which was reported as a protocol deviation.

Reviewer's comment: In response to an IR, The Applicant provided additional pregnancy data that were acquired from the study Sponsor subsequent to the database lock.

Elderly
A total of 16 subjects ≥65 years of age were enrolled in the study, including 11 in the placebo group and six in the V920 group. The following table describes the proportions of subjects reporting any adverse event, including solicited, unsolicited, and serious in the Year 1 time period.

Table 27 Number and proportions of geriatric subjects reporting adverse events in the Year 1 time period

MedDRA Preferred Term	V920 (N= 6) n (%)	Placebo (N= 11) n (%)
Nausea	1 (16.7)	0 (0)
Pyrexia	3 (50.0)	2 (18.2)

MedDRA Preferred Term	V920 (N= 6) n (%)	Placebo (N= 11) n (%)
Headache	2 (33.3)	3 (27.3)
Injection site pain	2 (33.3)	1 (9.1)
Myalgia	2 (33.3)	6 (54.6)
Cough	1 (16.7)	0 (0)
Decreased appetite	1(16.7)	0 (0)
Depression	1(16.7)	0 (0)
Fatigue	1 (16.7)	2 (18.2)
Malaria	1 (16.7)	3 (27.3)
Malignant hypertension	1 (16.7)	0 (0)
Arthralgia	0 (0)	3 (27.3)
Dizziness	0 (0)	1 (9.1)
Joint swelling	0 (0)	2 (18.2)

Source: ADAE dataset

SAEs were reported by three elderly subjects in each group, including events of malaria, depression, and malignant hypertension after V920 and three events of malaria after placebo.

Reviewer's comment: The frequency and pattern of adverse events in elderly subjects was consistent with observations in the subjects 18 to 64 years of age, although the limited numbers of subjects in each group precludes a robust analysis of safety in the ≥65 years of age group.

6.2.12.5 Adverse Events of Special Interest (AESI)

Joint events were solicited and analyzed separately; the analysis of these events included a subset of subjects (n= 201) who had data on joint events collected at Week 2. At the Week 1 visit, events of arthralgia were reported by 5.1% of subjects in the V920 group and 3.4% of subjects in the placebo group. Events of arthropathy and joint swelling were infrequent but were more common after V920 (0.6% and 0.2% of subjects, respectively) compared to placebo (0.2% and 0% of subjects, respectively). At Week 2, events of arthralgia were reported by 2% of subjects in the V920 group and 4% of subjects in the placebo group. For the time period through Month 1, including the Week 2 subset data, the proportions of subjects reporting a solicited term of arthralgia was 6.6% to 7.0% after V920 and 5.6% to 5.8% after placebo. The proportions of subjects reporting arthropathy, joint stiffness, and joint swelling were 0.6%, 0.4%, and 0.4%, respectively, after V920 and 0.2%, 0.2%, and 0.4%, respectively, after placebo.

Reviewer's comment: At Week 1, events of arthralgia, arthropathy, and joint swelling were reported by a higher proportion of subjects after V920, but the differences were small. As data on the severity and duration of the solicited systemic events of "Joint problems" (arthropathy, joint stiffness, and joint swelling) were not collected during the study, it is difficult to assess the impact of these symptoms on the daily functioning of affected subjects. Of the events of arthralgia and joint stiffness collected as general solicited events, all were mild in severity.

6.2.12.6 Clinical Test Results

At the Week 1 and Month 1 visits, the proportions of subjects with abnormalities in serum chemistry laboratories were generally comparable between the V920 and placebo groups.

At the Week 1 visit, the proportions of subjects with abnormalities in hematology laboratories were generally comparable. However, an imbalance was seen in the proportions of subjects with abnormalities in neutrophil counts. In the V920 group, 20.9% of subjects had Grade 1 (15.2% of subjects), 2 (4.6% of subjects), or 3 (1% of subjects) decreases in neutrophil count at the Week 1 visit compared to 9.7% of subjects in the placebo group with Grade 1 (7.3% of subjects), 2 (1.6% of subjects), or 3 (0.8% of subjects) decreases in neutrophil count. By the Month 1 visit, the proportion of subjects with abnormalities in neutrophil count was comparable between the groups and no other imbalances in hematologic abnormalities was noted.

In an assessment of changes from baseline, statistically significant differences between the V920 and placebo groups were observed for the following parameters: lymphocytes (4.7% V920 and 0.1% placebo), white blood cell count (-0.8 x 10^3/µL V920 and -0.1 x 10^3/µL placebo), neutrophils (-5.2% V920 and -0.8% placebo), red cell distribution width (-0.13% V920 and -0.02% placebo), and platelet count (-11.5 x 10^3/µL V920 and -2.6 x 10^3/µL).

Reviewer's comment: Information on statistical differences in hematology findings were presented in Kennedy, et al (2016) but were not described in the study CSR. Decreases in neutrophil count were observed in the mean change from baseline for the V920 group and also in a higher proportion of individual subjects after V920 compared to placebo; however, neutrophil count decreases were primarily Grade 1 to 2 and imbalances in neutrophil count abnormalities between the groups did not persist at the Month 1 visit.

6.2.12.7 Dropouts and/or Discontinuations
No subject discontinued the study due to an AE. At Week 1 and Month 1, safety data was available for >98% of subjects in each group.

6.2.13 Study Summary and Conclusions

V920-009 was originally designed as a Phase 2/3 randomized, double-blind, placebo-controlled safety and efficacy study of V920 and another Ebola candidate vaccine in adults 18 years of age and older; however, due to decreasing incidence of Ebola in Liberia, the study collected safety and immunogenicity data from 500 subjects in each treatment arm from a single treatment center. Humoral immune responses, as measured by GP-ELISA and PRNT, were demonstrated after V920 and in each subgroup (>50 years of age, HIV positive, and by gender). In the 1-month period following vaccination, injection site pain, fatigue, pyrexia, and myalgia were the most commonly reported solicited events in both the V920 and placebo groups but were more frequently reported after V920. The proportion of subjects reporting each unsolicited event were generally comparable. Serious adverse events and deaths were reported with similar frequency in each group, and there was no pattern of events to suggest a safety signal.

6.3 Trial #3

V920-012: 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-ZEBOVGP (V920 Ebola Vaccine) in Healthy Adults

First subject first visit: August 17, 2015
Date of last subject visit for 6-month timepoint: May 2, 2016
Date of last subject visit for 24-month report: September 29, 2017
Database lock for 6-month timepoint: April 19, 2017
Database lock for 24-month timepoint: February 28, 2018
Sponsor name: Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc.

6.3.1 Objectives

Primary objectives:

- To determine whether vaccination with V920 from three separate consistency lots results in equivalent immunogenicity.
- To determine the safety and tolerability of V920 from three Consistency Lot groups (A, B, and C each separately and combined) and a High Dose group through 42 days post-vaccination.

Secondary objectives:

- To determine whether vaccination with V920 from three separate Consistency Lots results in equivalent immunogenicity.
- To estimate the anti-ZEBOV GP-ELISA GMTs measured at 28 days post-vaccination in the three Consistency Lot groups (Lots A, B, and C combined) and the High Dose group.
- To estimate the GMTs of neutralizing antibodies measured by PRNT at 28 days post-vaccination in the three Consistency Lot groups (A, B, and C combined) and the High Dose group.

Other objectives:

- To estimate the anti-ZEBOV GP-ELISA and PRNT GMTs measured at 6 months post-vaccination in the three Consistency Lot groups (Lots A, B, and C combined) and the High Dose group.
- To determine the safety and tolerability of V920 from three Consistency Lot groups (A, B, and C each separately and combined) and the High Dose group for serious adverse events (SAEs) through 6 months post-vaccination.
- To estimate the anti-ZEBOV GP-ELISA and PRNT GMTs through 24 months post-vaccination in a subset of V920 recipients.
- To assess SAEs through 24 months post-vaccination in a subset of V920 recipients.

6.3.2 Design Overview

V920-012 was a randomized, placebo-controlled, multicenter, double-blind trial of V920 in healthy adult subjects 18 to 65 years of age. A total of 1125 subjects were planned for enrollment and randomization 2:2:2:2:1 to receive either a single vaccination from one of three consistency lots of V920 (≥2 x 10^7 pfu/dose), a High Dose lot of V920 (≥1x10^8 pfu/dose), or placebo (0.9% normal saline). The primary objectives of this study were the demonstration of consistency in the immune responses through 28 days post-vaccination of subjects receiving three separate consistency lots of V920 and the evaluation of safety of the consistency lots (separately and combined) and a High Dose lot (the upper threshold potency of the vaccine that would be used in the clinic) versus placebo. Immunogenicity and safety endpoints were evaluated for all subjects through 6

months post-vaccination. The base study was comprised of a 6-month period for assessment of the primary safety and immunogenicity objectives, with study site visits at Day 28, Day 42, and Month 6, followed by an extension through 24 months post-vaccination to evaluate the durability of immune response (anti-ZEBOV GP-ELISA and PRNT) and SAEs in a subset of subjects (n= 566). The extension trial design included 3 additional site visits at Months 12, 18, and 24 for collection of SAEs and serum for GP-ELISA and PRNT, as well as telephone calls at Months 15 and 21 to collect SAEs.

6.3.3 Population

Inclusion criteria: Healthy adult between 18 and 65 years of age who could provide informed consent and comply with study procedures and visits, including requirements for contraception.

Exclusion criteria: Was currently participating in or has participated in an interventional clinical trial with an investigational compound or device within 90 days of participation in this trial; prior receipt of Ebola vaccine or exposure to Ebola virus; pregnant or breastfeeding or planning to conceive within 2 months following study vaccination; direct household exposure to a pregnant or lactating woman at the time of participation or a person with known or suspected impairment of immunological function; fever (≥ 100.5ºF/38.0ºC) within 48 hours prior to study entry; received systemic corticosteroids (equivalent of ≥ 2 mg/kg total daily dose of prednisone or ≥20 mg/d for persons weighing >10 kg) for ≥14 consecutive days and had not completed treatment at least 30 days prior to study entry, received systemic corticosteroids exceeding physiologic replacement doses (~5 mg/d prednisone equivalent) within 14 days prior to study entry; received any live virus vaccine within 30 days prior to study entry or any non-live vaccine within 14 days prior to study entry; clinically significant history of intravenous drug abuse within 12 months prior to study entry; known allergy/sensitivity or contraindication to investigational product(s) or its/their excipients (e.g., albumin); history of malignancy ≤ 5 years prior to study entry except for adequately treated basal cell or squamous cell skin cancer or *in situ* cervical cancer; and/or a history or current evidence of any condition, therapy, lab abnormality or other circumstance that might expose the subject to risk by participating in the trial, confound the results of the study, or interfere with the subject's participation for the full duration of the study.

6.3.4 Study Treatments or Agents Mandated by the Protocol

The following table describes the study treatments for each group:

Table 28 Study treatments

Vaccine	Nominal Dose/ Potency	Actual Dose/ Potency	Route of Administration	Vaccination Regimen	Use
V920 rVSVΔG-ZEBOV-GP Consistency Lot A	≥2x10^7 pfu/dose*	6.6x10^7 pfu/dose*	IM	Single dose at Day 1 (Visit 1)	Investigational vaccine
V920 rVSVΔG-ZEBOV-GP Consistency Lot B	≥2x10^7 pfu/dose*	6.6x10^7 pfu/dose*	IM	Single dose at Day 1 (Visit 1)	Investigational vaccine
V920 rVSVΔG-ZEBOV-GP Consistency Lot C	≥2x10^7 pfu/dose*	5.4 x10^7 pfu/dose*	IM	Single dose at Day 1 (Visit 1)	Investigational vaccine
V920 rVSVΔG-ZEBOV-GP (High Dose)	≥1x10^8 pfu/dose**	2.4x10^8 pfu/dose**	IM	Single dose at Day 1 (Visit 1)	Investigational vaccine
Placebo	Normal saline (0.9%)	NA	IM	Single dose at Day 1 (Visit 1)	Placebo comparator

* The labels on the vaccine vials for Consistency Lots A, B, and C listed a potency of ≥2x10^7 pfu/dose, and the actual dose/potency measured for Consistency Lots A, B, and C is indicated. The vials of the V920 Consistency Lots A, B, and C were supplied as a single 1-mL dose.

** The labels on the vaccine vials for the High Dose Lot listed a potency of ≥1x10^8 pfu/dose, and the actual dose/potency measured for the High Dose Lot is indicated. The vials of the V920 High Dose Lot were supplied as a single 1-mL dose.

rVSVΔG-ZEBOV-GP=Recombinant vesicular stomatitis virus vaccine with *Zaire ebolavirus* glycoprotein

PFU=Plaque-forming units

IM=Intramuscular

NA=Not applicable

Source: Original BLA 125690/1; Clinical Study Report V920-012, p.56, Table 9-1

6.3.5 Directions for Use

Single dose of V920 or saline placebo administered IM.

6.3.6 Sites and Centers

This trial was conducted at 42 trial centers in the United States (n= 40), Canada (n= 1), and Spain (n= 1).

6.3.7 Surveillance/Monitoring

Follow up visits were scheduled for Day 28, Day 42, Month 3 (telephone only), and Month 6. A vaccine report card (VRC) prompted the subject to record his/her temperature and note any injection-site reactions during Days 1 to 42 post-vaccination. Subjects were specifically prompted for swelling, redness, pain/tenderness from Days 1 to 5 and joint pain, joint swelling, rashes and/or blisters from Days 1 to 42 in addition to blank spaces for unprompted recording of other complaints and illnesses (unsolicited adverse events). SAEs were collected for the duration of the 6-month follow-up period. Investigators reviewed all reported events of blisters and recorded either blisters or vesicles in the adverse event case report form (CRF). In the extension study, SAEs were collected at Months 12, 15, 18, 21, and 24.

Subjects with new onset rashes and/or vesicular lesions or new onset arthralgia and/or arthritis were instructed to contact the study site immediately. Additional laboratory testing for subjects with arthritis, rashes and/or vesicular lesions may have included (but were not limited to) the following: urinalysis, biopsy of skin (real-time V920 qRT-PCR and pathology), arthrocentesis (cell count with differential, culture, microscopy, real-time V920 qRT-PCR), and skin lesion swabs for real-time V920 qRT-PCR testing.

An eCRF was used to record all study data. An independent data monitoring committee was not utilized for this study.

6.3.9 Statistical Considerations & Statistical Analysis Plan

Sample size

For the primary hypothesis, this study had approximately 99% power to demonstrate equivalent immunogenicity across the consistency lots; even if one lot differed from the other two by 10%, with the following assumptions:

- 10% of the subjects enrolled in the study would be non-evaluable (~225 evaluable subjects in each V920 group and 112 evaluable subjects in the placebo group)
- the (within-lot) standard deviation (SD) on the log-scale of the GP-ELISA GMT was 1 (estimated from three Phase 1 studies)
- the true GP-ELISA GMT ratio between any two lots was 1, and 0.5-fold and 2.0-fold equivalence margins.

For the secondary hypothesis, this study had approximately 94% power to demonstrate equivalent immunogenicity across the consistency lots. The power and sample size were based on the same assumptions as the primary hypothesis but used 0.67-fold and 1.50-fold equivalence margins. The secondary hypothesis had approximately 81% power to demonstrate equivalent immunogenicity across the consistency lots if one lot differed from the other two by 10%.

Derived and transformed data

Safety data: For the analysis of solicited symptoms, missing or non-evaluable measurements were not replaced. For SAEs Days 1 to 42 and through Month 6), VRC-prompted injections site events Days 1 to 5) and elevated temperature (Days 1 to 42), arthralgia/arthritis (Days 5 to 42), petechial/purpuric rash (Days 5 to 42), and vesicular rash (Days 5 to 42), p-values and 95% CI were calculated. The time period of Day 5 to Day 42 was chosen for evaluation to avoid initial extraneous reactogenicity that occurs in the early days after any vaccination. For AEs reported by four or more subjects in either treatment group and solicited injection site reactions by maximum intensity or size, 95% CI were calculated. All statistical tests were conducted at the α=0.05 (2-sided) level. AEs were coded using MedDRA version 19.1.

Immunogenicity data: No imputation for missing data was performed. GP-ELISA values below the lower limit of quantification (LLOQ) were imputed to one-half the value of the LLOQ (i.e., 18.055 EU/mL).

For the assessment of humoral immunogenicity, the following applied:

- For GMTs and GMFRs, data were first log-transformed. The transformed data were then analyzed by ANOVA. The ANOVA statistics were then back-transformed into GMTs and GMFRs.
- Seroresponse statistics were based on frequencies.
- Subjects with a baseline GP-ELISA titer ≥200 EU/mL were considered seropositive at baseline.

Statistical analyses

For the primary analysis of lot-to-lot consistency, three pairwise comparisons of lots were made (Lot A to Lot B, Lot A to Lot C, and Lot B to Lot C). Each pairwise comparison of lots consisted of 2 one-sided tests of equivalence at the α=0.025 level. Equivalency was demonstrated if the two-sided 95% CI on the pairwise lot-to-lot comparison of the GP-ELISA GMT ratio was between 0.5-fold and 2.0-fold for the

primary analysis and between 0.67-fold and 1.5-fold for the secondary analysis. This procedure controlled the overall type I error at the two-sided 5% level because all three pairwise comparisons for consistency had to be satisfied; therefore, no multiplicity adjustment was required in order for the primary hypothesis to be considered successful. Summary statistics for the three consistency lots and hypothesis testing of the pairwise comparisons were based on an analysis of variance (ANOVA) model including consistency lot and age group as covariates.

For safety analyses, p-values and 95% CI for treatment comparisons were calculated for all serious and solicited events. For adverse events reported in four or more subjects in any vaccination group and the percentage of subjects with solicited injection-site adverse events by maximum intensity for pain and injection-site adverse events by maximum size for erythema and swelling, a 95% CI was calculated. For all other adverse events, only descriptive statistics were provided.

Analysis populations
See Section 6.3.10.1 (Populations Enrolled/Analyzed).

6.3.8 Endpoints and Criteria for Study Success

The endpoint for primary and secondary immunogenicity assessments measured by GP-ELISA was the GMT of antibody titers at Day 28 post-vaccination. The statistical success criterion for the primary objective of lot consistency required the 2-sided 95% CI on the pairwise lot-to-lot comparison of the GP-ELISA GMT ratio to be greater than than 0.5- fold but no more than 2.0-fold. The statistical success criterion for the secondary objective of lot consistency required the 2-sided 95% CI on the pairwise lot-to-lot comparison of the GP-ELISA GMT ratio to be greater than 0.67-fold but no more than 1.5-fold.

The endpoint for the secondary immunogenicity assessment was neutralizing antibodies measured by the $PRNT_{60}$ assay at 28 days post-vaccination in the Consistency Lot groups (A, B, and C combined) and the High Dose group.

The endpoints for the primary and secondary safety analyses included:

- SAEs (Day 1 to Day 42 and Day 1 to Month 6);
- injection site adverse events: redness, swelling, and pain/tenderness/soreness (Day 1 to Day 5) after any study vaccination;
- elevated temperature (≥38.0ºC [≥100.4°F] oral or equivalent) (Day 1 to Day 42);
- arthralgia and arthritis events (Day 5 to Day 42); and
- rash events (Day 1 to Day 42).

Reviewer's comment: Events of arthralgia/arthritis were collected from Day 1 to Day 42. However, the primary analysis of arthralgia/arthritis events occurring from Day 5 through 42 was chosen to exclude events that occurred in the initial reactogenicity period following vaccination. This focus may result in exclusion of events that are relevant to the understanding of the timing of onset and severity of this safety concern. Evaluation of events for both the Day 1-42 and the Day 5-42 time periods is included in the analyses of arthralgia/arthritis described in Section 6.3.12.5 below.

6.3.10 Study Population and Disposition.

6.3.10.1 Populations Enrolled/Analyzed

The Per-Protocol population (PP) was the primary population for the analysis of immunogenicity data and included all vaccinated subjects who satisfied the eligibility criteria, were seronegative at baseline (GP-ELISA < 200 EU/mL), have serum immunogenicity samples collected within the allowed window (+/- 3 days for Day 28), and did not have an important protocol deviation.

The Full Analysis Set (FAS) population includes all randomized subjects with serology data according to the treatment they actually received. The FAS was intended to serve as the secondary population for the analysis of serum antibody concentrations if >10% of the subjects were seropositive at baseline. This analysis was not conducted as <10% of subjects were seropositive at baseline.

The primary population for safety analysis was the All Subjects as Treated (ASaT) population and included all randomized subjects who received a dose of study vaccination. Subjects were included in the treatment group corresponding to the study vaccine they actually received for the analysis of safety data using the ASaT population.

6.3.10.1.1 Demographics

Table 29 Demographics

	V920 Lot A N= 266 n (%)	**V920 Lot B N= 265 n (%)**	**V920 Lot C N= 267 n (%)**	**V920 Combined Lots N= 798 n (%)**	**V920 High Dose N= 266 n (%)**	**Placebo N= 133 n (%)**	**Total N= 1197 n (%)**
Vaccinated	266 (100)	265 (100)	266 (99.6)	797 (99.9)	264 (99.2)	133 (100)	1194 (99.7)
Male	123 (46.2)	130 (49.1)	129 (48.3)	382 (47.9)	117 (44)	61 (45.9)	560 (46.8)
Female	143 (53.8)	135 (50.9)	138 (51.7)	416 (52.1)	149 (56)	72 (54.1)	637 (53.2)
Mean Age	41.3	41.5	40.9	41.2	41.7	41.1	41.3
SD	13.4	12.4	13.1	13.0	13.4	13.7	13.1
Median	43.0	41.0	40.0	42.0	42.0	40.0	42.0
Range	18 to 65	18 to 65	18 to 65	18 to 65	18 to 65	18 to 65	18 to 65
18-45 years of age	155 (58.3)	154 (58.1)	155 (58.1)	464 (58.1)	154 (57.9)	77 (57.9)	695 (58.1)
46-65 years of age	111 (41.7)	111 (41.9)	112 (41.9)	334 (41.9)	112 (42.1)	56 (42.1)	502 (41.9)
American Indian or Alaska Native	2 (0.8)	2 (0.8)	0 (0)	4 (0.5)	0 (0)	1 (0.8)	5 (0.4)
Asian	0 (0)	1 (0.4)	3 (1.1)	4 (0.5)	2 (0.8)	3 (2.3)	9 (0.8)
Black or African American	78 (29.3)	70 (26.4)	82 (30.7)	230 (28.8)	83 (31.2)	37 (27.8)	350 (29.2)
Multiple	3 (1.1)	4 (1.5)	7 (2.6)	14 (1.8)	2 (0.8)	1 (0.8)	17 (1.4)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.8)	1 (0.8)	3 (0.3)
White	183 (68.8)	188 (70.9)	175 (65.5)	546 (68.4)	177 (66.5)	90 (67.7)	813 (67.9)
Hispanic or Latino	34 (12.8)	37 (14)	45 (16.9)	116 (14.5)	36 (13.5)	21 (15.8)	173 (14.5)

	V920 Lot A N= 266 n (%)	V920 Lot B N= 265 n (%)	V920 Lot C N= 267 n (%)	V920 Combined Lots N= 798 n (%)	V920 High Dose N= 266 n (%)	Placebo N= 133 n (%)	Total N= 1197 n (%)
Not Hispanic or Latino	232 (87.2)	227 (85.7)	221 (82.8)	680 (85.2)	228 (85.7)	112 (84.2)	1020 (85.2)
Not reported	0 (0)	0 (0)	1 (0.4)	1 (0.1)	1 (0.4)	0 (0)	2 (0.2)
Unknown	0 (0)	1 (0.4)	0 (0)	1 (0.1)	1 (0.4)	0 (0)	2 (0.2)
Canada	5 (1.9)	5 (1.9)	6 (2.2)	16 (2)	6 (2.3)	2 (1.5)	24 (2)
Spain	9 (3.4)	8 (3.0)	10 (3.7)	27 (3.4)	9 (3.4)	4 (3.0)	40 (3.3)
United States	252 (94.7)	252 (95.1)	251 (94)	755 (94.6)	251 (94.4)	127 (95.5)	1133 (94.7)
Mean weight	87.4	84.2	88.8	86.8	83.9	86.2	86.1
SD	23.8	21.3	23.7	23	20	24.2	22.5
Median	82.9	80.1	84.4	82.5	82	83.4	82.6
Range	42 to 192	44 to 216	44 to 216	40 to 216	49 to 164	41 to 195	40 to 216

Source: Adapted from Original BLA 125690/1; Clinical Study Report V920-012, p.95-97, Table 10-3

The demographics for subjects who continued in the extension study were similar to the base study. Overall, 44.9% of subjects were male, 58.5% were between 18 and 45 years of age, most were Black or African American or White (24.2% and 72.4%, respectively), and 85.9% were not Hispanic or Latino.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Reviewer's comment: In general, the medical history conditions reported by ≥5% of subjects in 1 or more study groups were balanced across the study groups.

6.3.10.1.3 Subject Disposition

A total of 1197 subjects were enrolled in the study, 1194 of whom were vaccinated. The following table summarizes the disposition of all randomized subjects.

Table 30 Subject disposition (Randomized population)

	V920 Lot A N= 266 n (%)	V920 Lot B N= 265 n (%)	V920 Lot C N= 267 n (%)	V920 Combined Lots N= 798 n (%)	V920 High Dose N= 266 n (%)	Placebo N= 133 n (%)	Total N= 1197 n (%)
Vaccinated	266 (100)	265 (100)	266 (99.6)	797 (99.9)	264 (99.2)	133 (100)	1194 (99.7)
Day 1-42 Completed	258 (97.0)	263 (99.2)	262 (98.5)	783 (98.2)	259 (98.1)	132 (99.2)	1174 (98.3)
Day 1-42 Discontinued	8 (3.0)	2 (0.8)	4 (1.5)	14 (1.8)	5 (1.9)	1 (0.8)	20 (1.7)
Lost to follow up	5 (1.9)	1 (0.4)	4 (1.5)	10 (1.3)	4 (1.5)	1 (0.8)	14 (1.2)
Physician decision	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)
Withdrawal by subject	3 (1.1)	1 (0.4)	0 (0)	4 (0.5)	1 (0.4)	0 (0)	5 (0.4)
Day 43- Month 6 Completed	248 (96.1)	253 (96.2)	252 (96.2)	753 (96.2)	255 (98.5)	130 (98.5)	1138 (96.9)
Day 43- Month 6 Discontinued	10 (3.9)	10 (3.8)	10 (3.8)	30 (3.8)	4 (1.5)	2 (1.5)	36 (3.1)
Death	1 (0.4)	1 (0.4)	0 (0)	2 (0.3)	0 (0)	0 (0)	2 (0.2)
Lost to follow up	6 (2.3)	7 (2.7)	6 (2.3)	19 (2.4)	1 (0.4)	1 (0.8)	21 (1.8)

	V920 Lot A N= 266 n (%)	**V920 Lot B N= 265 n (%)**	**V920 Lot C N= 267 n (%)**	**V920 Combined Lots N= 798 n (%)**	**V920 High Dose N= 266 n (%)**	**Placebo N= 133 n (%)**	**Total N= 1197 n (%)**
Withdrawal by subject	3 (1.2)	2 (0.8)	4 (1.5)	9 (1.1)	3 (1.2)	1 (0.8)	13 (1.1)

Source: Adapted from Original BLA 125690/1; Clinical Study Report V920-012, p.83, Table 10-1

Reviewer's comment: The discontinuation rates and reasons for discontinuation were similar between the study groups.

PP immunogenicity analysis population: Of the 1194 randomized and vaccinated subjects, 1039 were included in the PP population and 154 subjects (12.9%) were excluded due to major protocol deviations deviation considered to have the potential to affect or confound the immunogenicity result. The most common reasons for exclusion included (subjects could have more than one reason for exclusion): vaccine temperature excursion (65 subjects; 5.4%), lack of clinical laboratory results at Visit 4 (56 subjects; 4.7%), Visit 4 completed outside of the protocol-specified window (54 subjects; 4.5%), and subject was positive to ZEBOV via GP-ELISA at baseline (31 subjects; 2.6%).

The proportion of subjects excluded from the PP analysis was between 10 and 15% in the Lot A, B, and C groups, 20.5% in the High Dose group, and 6.8% in the placebo group.

Reviewer's comment: The proportion of subjects excluded from the immunogenicity analyses was higher in the study vaccine groups compared to the placebo group, especially in the High Dose group. However, the proportion of subjects excluded in the Lot A, B, and C groups was comparable and is unlikely to affect interpretation of the primary and secondary lot equivalency assessments.

ASaT safety analysis population: Of the 1194 randomized and vaccinated subjects, 1184 were included in the ASaT population.

Reviewer's comment: In response to an IR, the Applicant indicated that the 10 subjects excluded from the ASaT population were lost to follow-up after Day 1 and did not provide any safety follow up. All 10 subjects were in the Combined Lots group (n= 6) or High Dose group (n= 4).

Compliance with safety follow up: Compliance with the VRC was not provided in the study datasets or CSR. The number of subjects in the population with safety follow up in the tabular summary of solicited events from Day 1 to 5 included all 1184 subjects in the ASaT population. Of the 1051 subjects in the V920 groups, 1045 (99.4%) had a Day 28 visit, 1042 (99.1%) had a Day 42 visit, and 1008 (95.9%) had a Month 6 visit. Of the 133 subjects in the V920 groups, 132 (99.2%) had a Day 28 visit, 132 (99.2%) had a Day 42 visit, and 130 (97.7%) had a Month 6 visit.

Trial extension population: Of the 566 subjects who elected to continue in the extension study, 55 (9.7%) discontinued. The most common reasons for discontinuation were lost to follow-up (5.1%) and withdrawal by subject (3.4%).

Protocol deviations: A total of 331 major protocol deviations were reported for 280 (23.5%) subjects. The following table describes the major protocol deviations:

Table 31 Major protocol deviations

Category	Protocol Deviation(s)	Number of Deviations
Clinical Supplies	Temperature excursion	65
	Incorrect study therapy	1
Visit Window	Non-compliance with immunogenicity specimen collection and/or safety follow-up scheduled windows	54
ICF	Subjects signed the wrong version of the main, FBR or extension ICF	25
	Subject did not give informed consent for collection of FBR specimens and FBR specimens were collected	4
	ICF was not signed by the site or the subject	4
	ICF contact fields left blank by the site	3
Prohibited medications	Subject received disallowed concomitant vaccination	27
	Subject received disallowed corticosteroid dose	1
Entry criteria	Subjects entered that did not satisfy the inclusion/exclusion criteria as stated in the protocol	11
GCP non-compliance	Study coordinator falsely reported the completion of Month 3 safety follow-up phone calls	6
Immunogenicity assessment	Failure to conduct major/significant protocol-specified immunogenicity assessments	3
Safety assessment	Noncompliance in transfer of VRC entries to the AE eCRF	75
	Non-compliance in completion of VRC	45
	Failure to follow guidance document for assessment and work-up of specific adverse events	5
	Subjects whose SAEs/AEs were not reported by the site in a timely manner to the sponsor	2

ICF= informed consent form; FBR= future biomedical research
Source: Adapted from text in Original BLA 125690/1; Clinical Study Report V920-012, p.84-86

The following actions were taken for study deviations:

- A temperature excursion occurred at the central storage and distribution facility, prior to clinical supply shipment to sites and subject randomization. This excursion affected 16 subjects prior to the Applicant's awareness. Temperature excursions occurred at two investigator sites that affected 49 subjects. The effects of these temperature excursions on the study vaccine could not be ruled out and therefore 65 subjects were excluded from the primary immunogenicity analysis.
- Informed consent form (ICF) protocol deviations were addressed by the site and subjects at subsequent visits (when possible).
- Another study coordinator repeated the Month 3 safety follow-up phone calls for 6 subjects with fraudulently reported data from that visit. The 6 subjects were included in safety and immunogenicity analyses for this trial after it was confirmed that no SAEs had occurred at Month 3. An audit of the site was conducted, and the audit sample consisted of 100% source data verification for all 8 subjects randomized at the site. There were sporadic, minor discrepancies noted between subjects' source documents versus that were captured in the database.
- Site monitors performed a 100% reconciliation of the VRC to the AE eCRF and ensured all VRC AEs were recorded in the AE eCRF.
- At the time of VRC collection at Day 42, the site asked if the subject had any AEs or felt feverish during days/periods for which VRC information was missing.

Events reported during this visit were recorded in the source document and entered into the eCRF.

Reviewer's comment: There were a high number of protocol deviations for this study. However, the sponsor appears to have adequately addressed issues with GCP compliance, ICF completion, and safety assessments. All 127 subjects with major protocol deviations in the safety assessment category were included in the ASaT population, which is acceptable given the methods to ensure the capture of safety data as described above.

6.3.11 Immunogenicity Analyses

6.3.11.1 Analysis of Primary Endpoint

Based on an ANOVA model with a response of the natural log of individual titers and fixed effects for lots and age group (18 to 45 years and 46 to 65 years), the estimated GMT for each Lot group at Day 28 is as follows:

- Lot A (n/N= 239/266): 1183.9 EU/mL
- Lot B (n/N= 231/264): 1266.0 EU/mL
- Lot C (n/N= 226/266): 1346.0 EU/mL

The estimated fold difference for each comparison is as follows:

- Lot A vs Lot B: 0.94 (95% CI: 0.77, 1.14)
- Lot A vs Lot C: 0.88 (95% CI: 0.71, 1.09)
- Lot B vs Lot C: 0.94 (95% CI: 0.77, 1.15)

The p-values for the comparison of the GMT ratio to the lower bound (0.5) and the upper bound (2.0) were <0.001 for all pairwise comparisons.

Reviewer's comment: The statistical success criterion for the primary endpoint was met as the two-sided 95% CI on the pairwise lot-to-lot comparison of the GP-ELISA GMT ratio was between 0.5 and 2.0-fold.

No analyses were performed on the Full Analysis Set (FAS) population because <10% of the subjects were seropositive at baseline.

6.3.11.2 Analyses of Secondary and Other Endpoints

Reviewer's comment: As per the data described in Section 6.3.11.1 (Analysis of Primary Endpoint) the statistical success criterion for the secondary endpoint immunogenicity analyses, was met as the two-sided 95% CI on the pairwise lot-to-lot comparison of the GP-ELISA GMT ratio was between 0.67 and 1.5-fold. CBER recommended this secondary endpoint to increase the stringency of the pre-specified lot-to-lot comparison success criterion.

The following table describes the anti-ZEBOV GP-ELISA GMTs measured at all time points post-vaccination in the Consistency Lot groups (Lots A, B, and C combined) and the High Dose group.

Table 32 Summary of GP-ELISA Geometric Mean Titers by Vaccination Group (Day 1 to Month 24)
(Per-Protocol Immunogenicity Population)

Assay Time Point	V920 Lot A (N=266) GMT (n) [95% CI]	V920 Lot B (N=264) GMT (n) [95% CI]	V920 Lot C (N=266) GMT (n) [95% CI]	V920 Combined Lots (N=796) GMT (n) [95% CI]	V920 High Dose (N=264) GMT (n) [95% CI]	Placebo (N=133) GMT (n) [95% CI]
GP-ELISA						
Day 1	< 36.11 (239) [<36.11, <36.11]	< 36.11 (231) [<36.11, <36.11]	< 36.11 (226) [<36.11, <36.11]	< 36.11 (696) [<36.11, <36.11]	< 36.11 (219) [<36.11, <36.11]	< 36.11 (124) [<36.11, <36.11]
Day 28	1,183.9 (239) [1,038.7, 1,349.4]	1,266.0 (231) [1,108.2, 1,446.2]	1,346.0 (226) [1,176.6, 1,539.9]	1,262.0 (696) [1,168.9, 1,362.6]	1,291.9 (219) [1,126.9, 1,481.2]	< 36.11 (124) [<36.11, <36.11]
Month 6	1,052.0 (226) [920.0, 1,203.0]	1,060.2 (221) [925.8, 1,214.2]	1,241.3 (217) [1,082.5, 1,423.4]	1,113.4 (664) [1,029.5, 1,204.0]	1,189.5 (215) [1,036.7, 1,364.9]	< 36.11 (123) [<36.11, <36.11]
Month 12	1,001.3 (107) [817.7, 1,226.1]	1,095.0 (117) [902.2, 1,329.0]	1,144.7 (103) [931.2, 1,407.1]	1,078.4 (327) [960.6, 1,210.7]	1,135.5 (116) [934.8, 1,379.3]	< 36.11 (65) [<36.11, <36.11]
Month 18	912.7 (105) [746.0, 1,116.6]	1,003.6 (109) [823.4, 1,223.2]	1,202.5 (100) [978.0, 1,478.6]	1,029.9 (314) [916.3, 1,157.5]	1,123.2 (111) [923.1, 1,366.5]	< 36.11 (65) [<36.11, <36.11]
Month 24	857.2 (102) [703.1, 1,045.1]	907.9 (105) [746.8, 1,103.7]	1,007.2 (96) [821.1, 1,235.5]	920.3 (303) [820.4, 1,032.3]	1,009.1 (105) [830.0, 1,226.7]	< 36.11 (65) [<36.11, <36.11]

The per-protocol immunogenicity population includes all subjects who were compliant with the protocol, received vaccination, were seronegative at Day 1, and had a serum sample at one or more timepoints collected within an acceptable day range.
N = Number of subjects with serology data at one or more timepoints according to the treatment to which they were randomized.
n = Number of subjects contributing to the analysis.
< 36.11 were replaced with 36.11/2 in GMT calculations.
CI = Confidence interval; GP-ELISA = Anti-Glycoprotein Human Enzyme-Linked Immunosorbent Assay (EU/mL); GMT = Geometric mean titer

Source: Original BLA 125690/1; Statistical Report (Final Results) V920-012, p. 28, Table 4-3

For all study vaccine groups, the GMFR in GP-ELISA titers from baseline was between 58.4 and 68.5 at Day 28 and between 52.1 and 63.5 at Month 6. In the extension study, the GMFRs decreased slowly over subsequent visits, but remained between 47.6 and 49.8 for all study vaccination groups at Month 24.

For all study vaccine groups, the seroconversion rate (defined as a 2-fold increase from baseline and ≥200 EU/mL for GP-ELISA) was between 97.3% and 99.5% at Day 28 and between 95.1% and 96.3% at Month 6. In the extension study, the GMFRs decreased slowly over subsequent visits, but remained between 92.1% and 93.3% for all study vaccination groups at Month 24. The proportions of subjects with a seroresponse (defined as ≥4-fold increase from baseline for GP-ELISA) were between 96.2% and 98.6% for all study vaccination groups at any time point through Month 24.

Reviewer's comment: Humoral immune responses as measured by GP-ELISA were generally comparable between the High Dose and Consistency lots. Peak responses were observed at Day 28. Decreases in GMT were noted through Month 24; however, the GMTs at Month 24 were between 72.9% and 78% of the Day 28 GMTs.

The following table describes the PRNT GMTs measured at all time points post-vaccination in the Consistency Lot groups (Lots A, B, and C combined) and the High Dose group.

Table 33 Summary of PRNT Geometric mean titers by vaccination group (Day 1 to Month 24)
(Per-Protocol Immunogenicity Population)

Assay Time Point	V920 Lot A (N=266) GMT (n) [95% CI]	V920 Lot B (N=264) GMT (n) [95% CI]	V920 Lot C (N=266) GMT (n) [95% CI]	V920 Combined Lots (N=796) GMT (n) [95% CI]	V920 High Dose (N=264) GMT (n) [95% CI]	Placebo (N=133) GMT (n) [95% CI]
PRNT						
Day 1	< 35 (239) [<35, <35]	< 35 (231) [<35, <35]	< 35 (226) [<35, <35]	< 35 (696) [<35, <35]	< 35 (219) [<35, <35]	< 35 (124) [<35, <35]
Day 28	185.5 (239) [163.8, 210.0]	196.1 (231) [172.9, 222.5]	228.2 (226) [200.9, 259.3]	202.1 (696) [187.9, 217.4]	236.1 (219) [207.4, 268.8]	< 35 (123) [<35, <35]
Month 6	246.9 (226) [217.5, 280.4]	263.6 (221) [231.8, 299.7]	291.7 (217) [256.2, 332.0]	266.5 (664) [247.4, 287.0]	302.1 (215) [265.2, 344.1]	< 35 (123) [<35, <35]
Month 12	257.4 (107) [212.7, 311.6]	260.1 (117) [216.7, 312.2]	301.1 (103) [247.8, 365.7]	271.4 (327) [243.4, 302.7]	323.7 (116) [269.5, 388.8]	< 35 (65) [<35, <35]
Month 18	255.3 (105) [211.5, 308.2]	256.9 (109) [213.6, 309.1]	327.3 (100) [269.9, 396.9]	276.9 (314) [248.3, 308.9]	365.0 (111) [304.0, 438.4]	< 35 (65) [<35, <35]
Month 24	266.8 (102) [220.1, 323.4]	255.7 (105) [211.5, 309.0]	282.4 (95) [231.4, 344.7]	267.6 (302) [239.4, 299.2]	342.5 (105) [283.4, 414.0]	< 35 (65) [<35, <35]

The per-protocol immunogenicity population includes all subjects who were compliant with the protocol, received vaccination, were seronegative at Day 1, and had a serum sample at one or more timepoints collected within an acceptable day range.
N = Number of subjects with serology data at one or more timepoints according to the treatment to which they were randomized.
n = Number of subjects contributing to the analysis.
< 35 were replaced with 35/2 in GMT calculations.
CI = Confidence interval; PRNT = Plaque Reduction Neutralization Test; GMT = Geometric mean titer

Source: Original BLA 125690/1; Statistical Report (Final Results) V920-012, p. 43, Table 4-7

The GMFR from baseline in PRNT titers was 11.4 in the Combined Lots group and 13.5 in the High Dose group at Day 28. The GMFR peaked at Month 18 in the Combined Lots and High Dose lot groups (15.8 and 20.9, respectively) and remained stable at the Month 24 visit (15.3 and 19.6, respectively). At each visit through Month 24, the proportion of subjects with a seroresponse (defined as a ≥4-fold increase from baseline for PRNT) post-vaccination was between 84.9% and 91.1% in the Combined Lots group and 90.4% and 97.1% in the High Dose lot group.

Reviewer's comment: PRNT responses were generally comparable between The High Dose and Consistency lot groups, although the GMTs were numerically higher in the High Dose group at every time point. The PRNT GMTs peaked later (Month 18) than the GP-ELISA GMTs (Day 28) and remained generally comparable to peak values at Month 24.

6.3.11.3 Subpopulation Analyses
The following table describes the immunogenicity subgroup analyses by age group and gender for the primary endpoint (Day 28) and Month 6.

Table 34 Summary of geometric mean titers (EU/mL), geometric mean fold-rise, and seroconversion rates for the Combined Lots by age group and gender (Day 28 and Month 6)

	Day 28 GMT (n) [95% CI]	**Day 28 GMFR (n) [95% CI]**	**Day 28 Sero-conversion Rate Percent (m/n) [95% CI]**	**Month 6 GMT (n) [95% CI]**	**Month 6 GMFR (n) [95% CI]**	**Month 6 Sero-conversion Rate Percent (m/n) [95% CI]**
18-45 years of age N= 462	1289.8 (403) [1166.1, 1426.6]	65.6 (403) [59.1, 72.9]	95.8 (386/403) [93.3, 97.5]	993.4 (384) [893.5, 1104.5]	50.9 (384) [45.6, 56.9]	94.0 (361/384) [91.1, 96.2]
46-65 years of age N= 334	1224.8 (293) [1087.7,]1379.2	62.2 (293) [55.0, 70.2]	94.9 (278/293) [91.7, 97.1]	1301.7 (280) [1161.2, 1459.2]	66.3 (280) [58.8, 74.7]	96.8 (271/280) [94.0, 98.5]

	Day 28 GMT (n) [95% CI]	Day 28 GMFR (n) [95% CI]	Day 28 Sero-conversion Rate Percent (m/n) [95% CI]	Month 6 GMT (n) [95% CI]	Month 6 GMFR (n) [95% CI]	Month 6 Sero-conversion Rate Percent (m/n) [95% CI]
Female N=416	1234.9 (369) [1105.5, 1379.6]	61.8 (369) [55.1, 69.3]	94.0 (347/369) [91.1, 96.2]	1191.5 (353) [1063.8, 1334.5]	59.8 (353) [53.1, 67,3]	94.1 (332/353) [91.0, 96.3]
Male N= 380	1293.3 (327) [1164.0, 1437.0]	66.9 (327) [60.0, 74.6]	96.9 (317/327) [94.4, 98.5]	1030.9 (311) [926.6, 1146.8]	53.8 (311) [48.1, 60.2]	96.5 (300/311) [93.8, 98.2]

N = Number of subjects with serology data at one or more timepoints according to the treatment to which they were randomized; m = Number of subjects seropositive; n = Number of subjects contributing to the analysis; GMT = Geometric mean titer; GMFR=Geometric Mean Fold Rise; CI = Confidence interval; GP-ELISA = Anti-Glycoprotein Human Enzyme-Linked Immunosorbent Assay (EU/mL)

Source: Adapted from original BLA 125690/1; Clinical Study Report V920-012, p. 268-279, Tables 14.2-2 through 14.2-13

The subpopulation analysis for the extension study demonstrated that subjects 46 to 65 years of age and females had slightly higher titers compared to younger subjects and males at Months 12, 18, and 24, although there was overlap in the 95% CI. At Month 24, the GP-ELISA GMT for the 46 to 65-year old subjects in the Combined Lots group was 989.3 [95% CI: 835.4, 1171.5] compared to 870.3 [95% CI: 744.0, 1018.1] for subjects 18-45 years of age. At Month 24, the GP-ELISA GMT for the female subjects in the Combined Lots group was 958.6 [95% CI: 814.0, 1128.8] compared to 875.3 [95% CI: 746.0, 1071.1] for male subjects.

Table 35 Summary of PRNT geometric mean titers, geometric mean fold-rise, and seroconversion rates for the Combined Lots by age group and gender (Day 28 and Month 6)

	Day 28 GMT (n) [95% CI]	Day 28 GMFR (n) [95% CI]	Day 28 Seroresponse Rate Percent (m/n) [95% CI]	Month 6 GMT (n) [95% CI]	Month 6 GMFR (n) [95% CI]	Month 6 Seroresponse Rate Percent (m/n) [95% CI]
18-45 years of age N= 462	212.7 (403) [193.2, 234.2]	12.0 (403) [10.8, 13.2]	85.9 (346/403) [82.1, 89.1]	244.4 (384) [220.8, 270.5]	13.7 (384) [12.4, 15.2]	86.5 (332/384) [82.6, 89.7]
46-65 years of age N= 334	188.4 (293) [168.5, 210.6]	10.8 (293) [9.6, 12.0]	83.6 (245/293) [78.9, 87.7]	300.1 (280) [269.9, 333.7]	17.1 (280) [15.4, 19.1]	95.4 (267/280) [92.2, 97.5]
Female N=416	200.4 (369) [181.0, 221.9]	14.1 (123) [11.8, 16.8]	83.7 (309/369) [79.6, 87.4]	298.8 (353) [260.6, 322.1]	16.5 (353) [14.9, 18.4]	90.9 (321/353) [87.4, 93.7]
Male N= 380	204.1 (327) [183.8, 226.5]	11.5 (327) [10.3, 12.8]	86.2 (282/327) [82.0, 89.8]	242.3 (311) [218.8, 268.3]	13.6 (311) [12.3, 15.1]	89.4 (278/311) [85.4, 92.6]

N = Number of subjects with serology data at one or more timepoints according to the treatment to which they were randomized; m = Number of subjects seroresponding; n = Number of subjects contributing to the analysis; GMT = Geometric mean titer; GMFR=Geometric Mean Fold Rise; CI = Confidence interval; PRNT= Plaque Reduction Neutralization Test

Source: Adapted from original BLA 125690/1; Statistical Report (Final Results) V920-012, p. 126-139, Tables 8-24 through 8-35

In the subpopulation analysis for the extension study, the PRNT GMTs were generally comparable across the age and gender groups at each time point, although the subjects 46-65 years of age and female subjects had slightly numerically higher GMT values.

Reviewer's comment: At Day 28, the GMTs as measured by GP-ELISA and PRNT were comparable across the age and gender subgroups. At Month 6, the GMT and GMFR were slightly higher in subjects 46 to 65 years of age and females compared to the younger subject and males. As there is no known correlate of protection for V920, the clinical implication of minor differences across subpopulations in humoral immunogenicity is unclear.

6.3.11.4 Dropouts and/or Discontinuations

As described above, subjects with major protocol deviations that were thought to impact the immunogenicity findings were excluded from the analyses. See Section 6.3.10.1.3 (Subject Disposition) for details on all subjects excluded from immunogenicity evaluations.

6.3.12 Safety Analyses

6.3.12.1 Methods

Solicited injection site events were collected using a VRC from Days 1 to 5 and included erythema, pain, and tenderness; blank fields were provided to record any additional injection site events. The VRC solicited daily temperatures, events of rash, vesicular lesions, arthralgia, and arthritis from Days 1 to 42. SAEs were collected for the duration of participation in the study (6 months or 24 months [extension sub-study only]).

6.3.12.2 Overview of Adverse Events

The following table provides an overview of adverse events for the time period Day 1 to Month 6.

Table 36 Summary of adverse events Day 1 to Month 6 (ASaT population)

Subjects in population with follow-up:	**V920 Lot A N= 265 n (%)**	**V920 Lot B N= 263 n (%)**	**V920 Lot C N= 263 n (%)**	**V920 Combined Lots N= 791 n (%)**	**V920 High Dose N= 260 n (%)**	**Placebo N= 133 n (%)**
With 1 or more AEs	222 (83.8)	218 (82.9)	214 (81.4)	654 (82.7)	220 (84.6)	60 (45.1)
With injection-site AEs	188 (70.9)	196 (74.5)	191 (72.6)	575 (72.7)	183 (70.4)	20 (15.0)
With non-injection site AEs	174 (65.7)	155 (58.9)	170 (64.6)	499 (63.1)	181 (69.6)	47 (35.3)
With SAEs	7 (2.6)	4 (1.5)	7 (2.7)	18 (2.3)	3 (1.2)	0 (0)
Who died	1 (0.4)	1 (0.4)	0 (0)	2 (0.3)	0 (0)	0 (0)

AE= adverse event; SAE= serious adverse event
Source: Adapted from Original BLA 125690/1; Clinical Study Report V920-0012, p.131, Table 12-3

Solicited adverse events (ASaT population)
Injection site events (Days 1 to 5): Overall, in the Day 1 to 5 time period, injection site events were reported by 72.3% of subjects in the Combined Lots group (70.2 to 74.5% of subjects in each lot group), 70.4% of subjects in the High Dose lot group, and 14.3% of subjects in the placebo group.

VRC-collected injection site events included pain, erythema, and swelling. Pain was the most commonly reported injection site event (70% of subjects in the Combined Lots group, 67.7% of subjects in the High Dose group, and 13.5% of subjects in the placebo group). Events of injection site erythema and swelling were more frequently reported in the Combined Lots group (13.6% and 16.6%, respectively) and the High Dose group (7.3% and 16.2%, respectively) compared to the placebo group (1.5% and 3%, respectively). A statistical analysis of injection site events demonstrated that while there was no significant difference between each lot group, significant differences were noted in the proportions of subjects in the Combined Lots and High Dose groups compared to placebo. Other injection site events reported by more than 1 subject in any V920 group (n= 1051) included bruising (six subjects), hypoesthesia (two subjects), impairment of movement (four subjects), pruritis (10 subjects), rash (two subjects), reaction (10 subjects), and warmth (seven subjects). With the exception of two subjects with bruising, none of these other injection site events were reported in the placebo group.

Injection site pain was the only event graded as severe; severe events of injection site pain were reported by 2.7 to 2.8% of subjects in the V920 Combined Lots and High Dose groups. No subjects in the placebo group reported severe injection site events. Two subjects (0.3%) in the Combined Lots group reported injection-site erythema of >10 cm (with a duration of 7 and 8 days, respectively). No subjects in the High Dose or placebo group reported injection-site erythema or swelling of >10 cm.

In the Day 1 to 42 time period, the proportions of subjects in the Combined Lot, High Dose lot, and placebo group reporting injection site events was 72.7%, 70.4%, and 15.0%, respectively.

Reviewer's comment: Injection site events were more commonly seen after V920 than placebo, with the majority of V920 recipients reporting injection site events. The most commonly reported injection site event was pain and severe events of pain were infrequent and only occurred following V920. There was no increased frequency or severity of injection site events to suggest that the High Dose formulation had increased local reactogenicity compared to the consistency lots.

Temperature (Days 1 to 42): The proportions of subjects reporting a maximum temperature ≥38°C were higher for the Combined Lots group (20.2%) and High Dose group (32.2%) compared with the placebo group (0.8%). The proportions of subjects reporting a maximum temperature ≥39°C were higher for the Combined Lots group (3.2%) and High Dose group (4.3%) compared with the placebo group (0.8%). Adverse events of pyrexia were reported by 21.2%, 29.2%, and 0.8% of subjects in the Combined Lots group, High Dose group, and placebo group, respectively.

The median number of days to onset for temperature ≥38°C was 2.0 days in the Combined Lots (range 1.0 to 41.0) and High Dose groups (range 1.0 to 39.0), compared to 15.0 days in the placebo group (range 7.0 to 35.0). The median duration of fever was

1.0 day across all treatment groups, with a range of 1.0 to 5.0 days in the Combined Lots and High Dose groups.

Reviewer's comment: Fever was commonly observed following administration of V920 and adverse events of pyrexia were reported by a higher proportion of subjects in the High Dose group compared to the Combined Lots group. Data on the onset and duration of fever were provided in response to an IR.

Solicited joint- and skin-related events are reviewed in Section 6.3.12.5 (Adverse Events of Special Interest).

Unsolicited adverse events

Overall, unsolicited adverse events, including SAEs, were reported by 52.2% of subjects in the Combined Lots group, 58.1% of subjects in the High Dose lot group, and 30.8% of subjects in the placebo group.

From Day 1 to 42, the most frequently reported (≥20% in any V920 group) unsolicited AE in the Combined Lots, High Dose, and placebo groups was headache (21.1%, 25.8%, and 11.3%, respectively). Other systemic AEs that occurred in ≥10% of more of subjects in any group were nausea, chills, fatigue, influenza-like illness, pain, and myalgia. The following table summarizes the proportions of subjects reporting unsolicited adverse events, including SAEs, reported by at least 1% of subjects in one or more study vaccine groups.

Table 37 Unsolicited adverse events reported by at least 1% of subjects in one or more study vaccine groups and by a higher proportion of subjects after V920 compared to placebo Days 1 to 42 (ASaT population)

MedDRA Preferred Term	V920 Combined Lots N=791 n (%)	V920 High Dose N=260 n (%)	Placebo N=133 n (%)
Headache	167 (21.1)	67 (25.8)	15 (11.3)
Pain	86 (10.9)	33 (12.7)	2 (1.5)
Chills	50 (6.3)	27 (10.4)	1 (0.8)
Fatigue	45 (5.7)	20 (7.7)	3 (2.3)
Influenza like illness	44 (5.6)	9 (3.5)	1 (0.8)
Nausea	40 (5.1)	14 (5.4)	1 (0.8)
Myalgia	40 (5.1)	23 (8.8)	1 (0.8)
Back pain	32 (4.0)	10 (3.8)	1 (0.8)
Diarrhea	27 (3.4)	12 (4.6)	2 (1.5)
Pain in extremity	25 (3.2)	10 (3.8)	0 (0)
Oropharyngeal pain	21 (2.7)	8 (3.1)	3 (2.3)
Malaise	16 (2.0)	7 (2.7)	0 (0)
Dizziness	15 (1.9)	8 (3.1)	3 (2.3)
Vomiting	13 (1.6)	8 (3.1)	0 (0)
Muscle spasms	12 (1.5)	1 (0.4)	0 (0)
Nasopharyngitis	12 (1.5)	5 (1.9)	1 (0.8)
Body temperature increased	11 (1.4)	3 (1.2)	0 (0)
Decreased appetite	10 (1.3)	3 (1.2)	0 (0)
Paraesthesia	10 (1.3)	5 (1.9)	0 (0)
Peripheral swelling	10 (1.3)	2 (0.8)	0 (0)
Rhinorrhea	10 (1.3)	0 (0)	0 (0)
Musculoskeletal pain	10 (1.3)	5 (1.9)	1 (0.8)
Asthenia	9 (1.1)	3 (1.2)	1 (0.8)
Musculoskeletal stiffness	8 (1.0)	4 (1.5)	0 (0)

MedDRA Preferred Term	V920 Combined Lots N=791 n (%)	V920 High Dose N=260 n (%)	Placebo N=133 n (%)
Hypoaesthesia	7 (0.9)	4 (1.5)	0 (0)
Lethargy	5 (0.6)	6 (2.3)	0 (0)
Hyperhidrosis	4 (0.5)	3 (1.2)	1 (0.8)
Urinary tract infection	2 (0.3)	4 (1.5)	1 (0.8)

Source: Original BLA 125690/1; Clinical Study Report V920-012, p. 337-349, Table 14.3-17; and Amendment 37, response to IR Table1

Reviewer's comment: A tabular summary of unsolicited events excluding solicited joint and skin events was provided by the Applicant in response to an IR. The pattern of the most commonly reported unsolicited adverse events is consistent with increased systemic reactogenicity following V920 compared to placebo. Small imbalances in the proportions of subjects reporting unsolicited adverse events between the High Dose and Combined Lots groups may suggest that some systemic events are increased after receipt of a higher dose. Paraesthesias, which are not typically considered a feature of post-vaccination reactogenicity, were reported only after V920. Most events were mostly mild to moderate in severity, with the exception of one severe event. The time to onset ranged from 2 to 25 days, with a median of 13 days, and a median duration of 4.0-15.0 days.

In the Day 1 to 42 time period, severe unsolicited events were reported by a higher proportion of subjects in the Combined Lots group (9.2% of subjects) and High Dose group (12.3% of subjects) compared to the placebo group (1.5% of subjects). Severe systemic events reported by more than 1% of subjects in the Combined Lots group, the High Dose group or the placebo group included vomiting (0.3%, 1.2%, and 0% of subjects, respectively), chills (0.8%, 1.2%, and 0% of subjects, respectively), fatigue (0.8%, 1.9%, and 0% of subjects, respectively), influenza like illness (0.9%, 1.2%, and 0% of subjects, respectively), pain (1.1%, 0.8%, and 0% of subjects, respectively), pyrexia (1.5%, 2.3%, and 0% of subjects, respectively), myalgia (0.4%, 1.2%, and 0% of subjects, respectively), dizziness (0.3%, 1.5%, and 0% of subjects, respectively), and headache (3.0%, 3.5%, and 0% of subjects, respectively).

Reviewer comments: The most commonly reported severe systemic events (>1% of subjects in any group) were exclusively reported after administration of V920, were generally reported more frequently in the High Dose group, and were events that are consistent with systemic reactogenicity due to V920.

The median duration of severe pyrexia from Day 1 to Day 42 was 2 days for subjects in the Combined Lots group (range 0.2 to 4) and subjects in the High Dose group (range 0.3 to 3). The median duration of gastrointestinal events (abdominal pain and discomfort, diarrhea, nausea, and vomiting) was between 1.0 and 5.0 days in the Combined Lots and High Dose groups. The median duration of events of dizziness, headache, chills, fatigue, Influenza-like illness, malaise, myalgia, body temperature increased, and pain was between 1.0 and 3.0 days in the Combined Lots and High Dose groups.

Reviewer's comment: The Applicant provided an analysis of the duration of the most common unsolicited adverse events in response to an IR.

In the Day 1 to 42 time period, vaccine-related systemic adverse events were reported by 53% and 61.2% of subjects in the Combined Lots and High Dose groups,

respectively, compared to 14.3% of subjects in the placebo group. The most frequently reported vaccine-related systemic AEs from Day 1 to Day 42 were similar to those reported for all systemic AEs, including pyrexia, headache, and arthralgia, all of which were reported more commonly after V920 than placebo.

Reviewer's comment: Systemic reactogenicity, most commonly pyrexia and headache, was observed following V920, including severe events in 9.2% of subjects in Combined Lots group. A mild event of erythema multiforme was reported by a 29-year old female in the Lot C group 2 days after V920 that was considered related to study product. No additional details were provided for this event. This subject also reported mild vaginal lesion and moderate vaginal itch on Day 7 post-vaccination.

Concomitant medication use: The proportions of subjects who used any concomitant medication between Days 1 and 42 were 42.5%, 43.9%, and 27.1% in the Combined Lots, High Dose, and placebo groups, respectively. The most commonly reported concomitant medications included analgesics (used by 18.2%, 17.8%, and 9.8% of subjects in the Combined Lots, High Dose, and placebo groups, respectively) and anti-inflammatory and anti-rheumatic products (used by 22.3%, 26.5%, and 11.3% of subjects in the Combined Lots, High Dose, and placebo groups, respectively).

Pregnancy: A total of five pregnancies with a last menstrual period (LMP) through the Month 6 period were reported. Of the three pregnancies with a known outcome, two resulted in live births and one resulted in a spontaneous abortion.

- A 30-year old female in the V920 Lot C group with a history of dysmenorrhea and prior spontaneous abortion reported an SAE of spontaneous abortion at Week 4 of pregnancy 35 days after vaccination. The subject did not see a medical provider for the positive pregnancy test or for the spontaneous abortion.
- A 26-year old female in the V920 Lot A group became pregnant with an LMP 6 days after vaccination. A female infant was delivered via spontaneous vaginal delivery at 36 weeks gestational age.
- A 27-year old female in the V920 Lot B group became pregnant with an LMP 37 days after vaccination. A full-term female infant was delivered via vaginal delivery.

The outcome of the pregnancy is unknown for the remaining two reported pregnancies:

- A 22-year old female in the V920 Lot A group was vaccinated on (b) (6) , with an LMP reported in (b) (6) . On an unknown date in 2015, the pregnancy was confirmed by a positive pregnancy test. An estimated delivery date was reported as (b) (6) . This subject was lost to follow-up.
- A 43-year old in the V920 Lot B group became pregnant with an LMP 11 days prior to vaccination. The estimated date delivery was reported as (b) (6) . The outcome of the pregnancy is unknown.

Reviewer's comment: In response to an IR regarding discrepancies noted between SDTM datasets, the CSR, and the CIOMs reports, the sponsor provided clarification on the reported pregnancies and an updated summary of all pregnancies reported during the study. Of the five pregnancies reported with onset between Days 1 and 42, a spontaneous abortion was reported, although the pregnancy was not medically confirmed. No pattern of pregnancy-related outcomes was observed in this study, but the number of pregnancies is too small to inform a full understanding of the risks related to vaccine exposure prior to or after pregnancy.

An additional five pregnancies were reported in randomized and vaccinated subjects with an LMP date after Month 6 and a pregnancy was reported by a randomized and vaccinated subject who was unaware that they were pregnant until a spontaneous abortion occurred on Day 261 post-vaccination. The LMP date was not reported. Reported outcomes for these pregnancies included spontaneous abortion/miscarriage (n= 2), live birth (n= 2), and ruptured left ectopic pregnancy (n= 1).

6.3.12.3 Deaths

Two fatal SAEs were reported during the base study, both of which were not considered related to V920.

- A 64-year old female in the V920 Lot A group reported an SAE of craniocerebral injury due to a fall on Day 152 and died on Day 164 due to intracranial hemorrhage and traumatic brain injury.
- A 47-year old male in the V920 Lot B group with a history of alcoholism, alcoholic pancreatitis, gastroesophageal reflux disease, diabetes mellitus, peripheral neuropathy, hypertension, and hypothyroidism reported an SAE of hepatic failure on Day 76. Radiologic testing revealed cirrhosis and splenomegaly and laboratory testing was positive for Hepatitis C antibody. On Day 116, the subject died due to hepatic failure.

An additional fatal SAE of road traffic accident was reported in the extension study with a relative day of onset on Day 688 by a 52-year old subject in the Consistency Lot A group.

Reviewer's comment: The fatal events had clear alternative etiologies and were not temporally related to V920 administration; the assessment that the events were not related to V920 is appropriate.

6.3.12.4 Nonfatal Serious Adverse Events

A total of six non-fatal SAEs were reported in the Days 1-42 time period, all of which occurred in subjects in the Combined Lots group and none of which were considered related. The SAEs included:

- A 53-year old female with an undisclosed prior history of Graves disease and hyperthyroidism in the V920 Lot A group reported an SAE of worsening of hyperthyroidism (free thyroxine 4.6 ng/dL [normal high 1.1]) on the day following vaccination that necessitated hospitalization. After initiation of therapy, the subject was discharged home after a three-day hospitalization. She was subsequently evaluated in the emergency department three times with worsening hyperthyroidism.
- A 49-year old male with a history of overweight, osteoarthritis, hypertension, and hypogonadism in the V920 Lot C group reported an SAE of pulmonary embolism 22 days following vaccination. The subject was seen in the emergency department with chest pain and shortness of breath, at which time radiography revealed a pulmonary embolism and he was treated with warfarin sodium and enoxaparin sodium and discharged home.

- A 46-year old female with a history of asthma in the V920 Lot C group reported an SAE of asthma 15 days following vaccination. The subject was hospitalized for three days.
- A 37-year old female with a history of Type 2 diabetes mellitus in the V920 Lot B group reported an SAE of diabetic hyperosmolar non-ketotic state 22 days after vaccination. Concomitant medication included metformin. The subject presented with polyuria, polydipsia, nocturia and weakness. In the emergency department, the blood sugar was 607 mg/dL without ketones present. The subject was hospitalized for 2 days and treated with insulin and metformin. This subject also reported an SAE of urinary tract infection on Day 135.
- A 29-year old man with a history of kidney stones in the V920 Lot C group reported an SAE of right lower quadrant pain 38 days after vaccination. Radiography revealed ureteral and kidney calculi and a partial volvulus. The creatinine was elevated to 2.4 mg/dL on admission. A laparoscopic appendectomy was performed but the appendix was normal, and the principal investigator attributed the abdominal pain to the kidney stones. The subject was hospitalized for one day with resolution of abdominal pain and improvement in renal function.
- A 30-year old female in the V920 Lot C group reported a spontaneous abortion that is reviewed in Section 6.3.12.2 (Overview of Adverse Events).

Reviewer's comment: The non-fatal SAEs with time to onset within 42 days following vaccination were reported in subjects with a previous history of the condition or risk factors for the event. There was no pattern of events to suggest a specific safety signal.

An additional 13 subjects reported 15 non-fatal SAEs between Day 42 and Month 6, all of which occurred in subjects in the Combined Lots group and the High Dose group and none of which were considered related.

- Basal cell carcinoma was reported by a 61-year old male in the V920 Lot C group and a 59-year old male in the High Dose group at Days 106 and 143, respectively.
- Musculoskeletal events included spinal column stenosis reported on Day 161 by a 58-year old male in the V920 Lot B group; tibial exostosis reported on Day 65 by a 48-year old male in the V920 Lot A group that required surgical removal on Day 193; musculoskeletal chest pain reported on Day 113 by a 40-year old female in the V920 Lot C group; and a femur fracture due to a fall reported on Day 99 by a 56-year old female with osteopenia.
- A 33-year old female in the V920 Lot A group reported events of upper respiratory infection and pneumonia on Days 136 and 146, respectively, followed by an event of gastrointestinal disorder on Day 174, which was described as an abdominal ulcer located "behind an incision" from a previous gastric bypass surgery. At the 6-month follow-up call on Day 240, the subject also reported an event of hypoxia, for which no additional information is available.
- A 49-year old female in the V920 Lot A group reported an event of migraine on Day 51 that resulted in a three-day hospitalization, during which brain imaging was normal.
- A 26-year old male in the V920 Lot A group reported an event of hypertension on Day 77. The subject was observed for a day due to a blood pressure of 170/130

mmHg after consuming two pints of liquor; the subject was diagnosed with alcohol withdrawal syndrome.

- A 45-year old female in the V920 Lot B group with a history of goiter reported an event of autoimmune thyroiditis on Day 50.
- A 34-year old female in the High Dose group with a prolonged history of gastroesophageal reflux was hospitalized on Day 172 for a Nissen fundoplication for an event of gastroesophageal reflux disease.
- A 33-year old female in the V920 Lot C group reported an event of pulmonary embolism on Day 86. Concomitant therapies included etonogestrel implant, ethinyl estradiol, and norethindrone acetate.
- A 29-year old female in the V920 Lot C group reported events of arthropod bite and *Clostridium difficile* infection on Days 226 and 239 (at the time the Month 6 follow up call was conducted).

Reviewer's comment: Many of the non-fatal SAEs with time to onset between 42 days and 6 months following vaccination were reported in subjects with a previous history of the condition or risk factors for the event, or the SAE had a clear alternative etiology. For the Day 1 to Month 6 time period, SAEs reported by more than 1 subject included pulmonary embolism (n= 2), basal cell carcinoma (n= 2), and thyroid conditions (n=2). There was no clear evidence to support causality of V920 for these events, as they were all associated with pre-existing disease, known risk factors for disease, or a time to onset that was not suggestive of causality. Additional discussion of events of pulmonary embolism in the context of the entire clinical development program is in Section 8.4.8 (Adverse Events of Special Interest).

In the extension study, an additional 26 subjects reported unrelated non-fatal SAEs from Month 6 to Month 24 post-vaccination; 17 in the Combined Lots group (five, eight, and four for Consistency Lots A, B, and C, respectively), five in the High Dose lot group, and four in the placebo group. In the Consistency Lot A group, subjects reported the following SAEs: oropharyngeal squamous cell carcinoma; abortion spontaneous; two episodes of diverticulitis and deep vein thrombosis; exostosis and cellulitis; and hemothorax, pneumothorax, rib fracture, and scapula fracture. In the Consistency Lot B group, subjects reported the following SAEs: angioedema; mastitis; animal bite and abortion spontaneous; foot deformity; nephrolithiasis; incarcerated umbilical hernia; menometrorrhagia; and back pain. In the Consistency Lot C group, subjects reported the following SAEs: appendicitis, autoimmune thyroiditis, cholecystitis, and conductive deafness. In the High Dose lot group, subjects reported the following SAEs: suicidal ideation, breast cancer, radicular pain, schizophrenia, and ruptured ectopic pregnancy. In the placebo group, subjects reported the following SAEs: abortion spontaneous, arthropod bite and platelet count decreased; breast cancer Stage III; and meningitis aseptic, abdominal incarcerated hernia, and respiratory failure.

Reviewer's comment: The Applicant provided CIOMs for the SAEs reported in the extension study in response to an IR. The pattern of SAEs reported in the extension study is consistent with expected adverse events in adults and there is no pattern of events to suggest a safety signal of events with a long latency.

6.3.12.5 Adverse Events of Special Interest (AESI)

The study protocol predefined arthralgia, arthritis, rash, and vesicular lesions as AEs of

special interest. Subjects were prompted on the VRC to record arthralgia, arthritis, rashes and vesicular lesions (as "blisters") from Days 1 to 42. Composite terms for arthritis and rash were defined using blinded safety data before database lock. The following MedDRA PTs were used to define the composite term for arthritis: arthritis, monoarthritis, polyarthritis, osteoarthritis, joint swelling, or joint effusion. The following MedDRA PTs were used to define the composite term for rash: petechiae, purpura, rash, rash generalized, rash macular, rash papular, and rash vesicular. Based on reports of cutaneous vasculitis, petechiae, and purpura in a Phase 1 study, the following MedDRA PTs were also used: vasculitis, petechiae, and purpura. Composite terms were not generated for arthralgia or vesicular lesions.

Joint events

Events of arthritis and arthralgia were analyzed for the time periods of Days 1 to 42 and Day 5-24. The following table describes the proportions of subjects reporting arthralgia and arthritis events and the median time to onset and duration of events.

Table 38 Proportions of subjects with joint events, time to onset of joint events, and duration of joint events by study group and time period (ASaT population)

		Combined Lots Group N= 791	**High Dose Group N= 260**	**Placebo N=133**
Arthralgia Days 1-42	n (%)	135 (17.1)	53 (20.4)	4 (3.0)
	Severe events n (%)	6 (0.8)	8 (3.1)	0 (0)
	Median TTO	2.0	2.0	5.5
	Median duration	3.0	3.0	3.0
Arthralgia Days 5-42	n (%)	47 (5.9)	20 (7.7)	2 (1.5)
	Median duration	8.0	6.5	2.0
Arthritis Days 1-42	n (%)	39 (4.9)	12 (4.6)	0 (0)
	Severe events n (%)	5 (0.6)	3 (1.2)	0 (0)
	Median TTO	11.0	10.0	N/A
	Median duration	6.0	5.0	N/A
Arthritis Days 5-42	n (%)	29 (3.7)	8 (3.1)	0 (0)
	Median duration	7.5	5	N/A

TTO: time to onset (days); median duration and TTO in days; n= number of subjects

Source: Original BLA 125690/1; Clinical Study Report V920-012, Tables 14.3-31, 14.3-44, and 14.3-45.

One of three subjects with synovial fluid tested via RT-PCR for vaccine virus had positive results (2301 copies/mL at Day 17).

A statistical analysis of events from Day 5 to 42 demonstrated a significantly higher incidence of arthralgia and arthritis events in the V920 groups compared to the placebo group.

Reviewer's comment: Events of arthralgia and arthritis were reported more frequently after V920 and placebo. Arthralgia was reported more frequently by subjects in the High Dose lots compared to the Combined Lots; however, there was no evidence to suggest a dose relationship with events of arthritis. As discussed above, the sponsor performed an analysis of events on Days 5-42 to exclude events exclude events that occurred in the initial reactogenicity period following vaccination. After Day 5, the proportions of subjects reporting arthralgia and arthritis in the Combined Lots group was 5.9% and

3.7%, respectively, compared to 1.5% and 0%, respectively, in the placebo group. Factors favoring a phenomenon of V920 related joint events include: an imbalance in the proportions of subjects with arthralgia and arthritis (including severe events) after V920 compared to placebo and the occurrence of events after the immediate reactogenicity period, including an event associated with a positive PCR for vaccine virus in the synovial fluid at Day 17.

The following table describes the subgroup analysis of arthralgia and arthritis events by age, gender, and race.

Table 39 Proportions of subjects with joint events (Days 5-42) by age, gender, and race

		Combined Lots Group N= 791	**High Dose Group N= 260**	**Placebo N=133**
Arthralgia Days 5-42	Age 18-45 years n/N (%)	14/457 (3.1)	10/152 (6.6)	1/77 (1.3)
	Age 46-65 years n/N (%)	33/334 (9.9)	10/108 (9.3)	1/56 (1.8)
	Male n/N (%)	17/378 (4.5)	7/113 (6.2)	1/61 (1.6)
	Female n/N (%)	30/413 (7.3)	13/147 (8.8)	1/72 (1.4)
	White n/N (%)	43/542 (7.9)	17/175 (9.7)	2/90 (2.2)
	Non-white n/N (%)	4/259 (1.6)	3/85 (3.5)	0/43 (0)
Arthritis Days 5-42	Age 18-45 years n/N (%)	10/457 (2.2)	3/152 (2.0)	0/77 (0)
	Age 46-65 years n/N (%)	19/334 (5.7)	5/108 (4.6)	0/56 (0)
	Male n/N (%)	9/378 (2.4)	3/113 (2.7)	0/61 (0)
	Female n/N (%)	20/413 (4.8)	5/147 (3.4)	0/72 (0)
	White n/N (%)	24/542 (4.4)	8/157 (4.6)	0/90 (0)
	Non-white n/N (%)	5/249 (2.0)	0/85 (0)	0/43 (0)

n= number of subjects with one or more event; N= number of subjects in ASaT population with follow-up
Source: Original BLA 125690/1; Clinical Study Report V920-012, p. 643-651 and 659-666, Tables 14.3-48 through 53, Tables 14.3-57 through 62

Reviewer's comment: Post-vaccination arthralgia and arthritis were reported by a higher proportion of older, female, and White subjects compared to younger, male, and Non-white subjects, respectively.

In a *post-hoc* analysis of baseline variables associated with arthritis (Days 1 to 42), cross tabulations of counts and percentages, multivariate logistic regression, and multivariate logistic regression with random effect for investigator were used to determine the association between the covariates and arthritis (including: arthritis, monoarthritis, polyarthritis, osteoarthritis, joint swelling, or joint effusion). The baseline variables assessed include race, sex, age group, and medical history of arthritis for cross-tabulations and treatment dose, body mass index (BMI), age group, sex, medical history, and race for multivariate analyses. In these analyses, female sex and a positive medical history of arthritis were associated with a 2.2- to 2.8-fold higher risk of post-vaccination arthritis and 95% CI lower bounds of 1.1 and 1.3, respectively.

Rash events:
The following table describes rash events.

Table 40 Rash events by groups by age (Days 1-42)

Event	Combined Lots Group	High Dose Group	Placebo
Rash (composite term) n/N (%)	30/791 (3.8)	10/260 (3.8)	2/133 (1.5)
Rash (composite term) Age 18-45 years n/N (%)	19/457 (4.2)	7/152 (4.6)	1/77 (1.3)
Rash (composite term) Age 46-65 years n/N (%)	11/334 (3.3)	3/108 (2.8)	1/56 (1.8)
Petechiae n/N (%)	0/791 (0)	1/260 (0.4)	0/133 (0)
Rash n/N (%)	18/791 (2.3)	3/260 (1.2)	2/133 (1.5)
Rash macular n/N (%)	6/791 (0.8)	1/260 (0.4)	0/133 (0)
Rash papular n/N (%)	2/791 (0.3)	3/260 (1.2)	0/133 (0)
Rash vesicular n/N (%)	4/791 (0.5)	2/260 (0.8)	0/133 (0)
Blisters n/N (%)	8/791 (1.0)	2/260 (0.8)	0/133 (0)

n= number of subjects with one or more event; N= number of subjects in ASaT population with follow-up
Source: Original BLA 125690/1; Clinical Study Report V920-012, p. 630-633, Tables 14.3-41 through 42

RT-PCR testing for vaccine virus conducted on skin biopsies from six subjects was positive in one subject in the Consistency Lot B group (60 copies/mL at Day 14). This subject had a moderate AE of dermatitis on Day 6, which resolved spontaneously without treatment on Day 18. RT-PCR testing for vaccine virus conducted on subjects with vesicular lesions (n= 2) or blisters (n= 1) was positive for the subject with blisters (687160 copies/mL on Day 12).

Reviewer's comment: Skin-related AEs that were excluded from the composite term rash included rash maculo-papular and rash pruritic, each of which were reported by one subject after V920. Factors favoring a phenomenon of V920-related skin events include: an imbalance in the proportions of subjects with rash after V920 compared to placebo and 2 events of rash associated with positive PCR for vaccine virus in a skin biopsy and blister fluid.

6.3.12.6 Clinical Test Results

Routine laboratory testing was not obtained in this study. However, additional laboratory testing due to the occurrence of AEs was performed for 72 subjects. Of the 54 subjects with C-reactive protein testing, 17 had elevations. Of the 38 subjects with alanine aminotransferase testing, six had mild to moderate elevations.

Reviewer's comment: The Applicant provided individual listings for laboratory values in response to an IR. As laboratories were drawn based on clinical concerns, there is no available comparator data. C- reactive protein elevations that were temporally related to vaccination were observed, which may reflect a systemic response to a live, replicating vaccine.

6.3.12.7 Dropouts and/or Discontinuations

The ASaT safety analysis population included 1193 randomized and vaccinated subjects. The number of subjects with safety follow-up was 1184.

Reviewer's comment: Discontinuation rates were low across the study and comparable between study groups. It is unlikely that the discontinuation rate would have a major impact on safety.

6.3.13 Study Summary and Conclusions

V920-012 was a Phase 3, randomized, double-blinded, placebo-controlled clinical trial to study the safety and immunogenicity of three consistency lots and a High Dose lot of V920 in healthy adults. The GMT of anti-ZEBOV glycoprotein antibody measured by GP-ELISA at 28 days post-vaccination met statistical success criteria for the primary and secondary endpoints of lot consistency (two-sided 95% CI on the pairwise lot-to-lot comparison of the GP-ELISA GMT ratio of >0.5-fold and < 2.0-fold and >0.67-fold and <1.5-fold, respectively). Humoral immunogenicity as measured by GP-ELISA and PRNT was demonstrated at each post-vaccination time point, with a peak in GP-ELISA GMT at Day 28 and a peak in PRNT GMT at Month 18. Humoral immune responses continued to be detectable at Month 24.

Injection site events were more commonly seen after V920 than placebo, with the majority of V920 recipients reporting injection site events. The most commonly reported injection site event was pain, and severe events of pain were infrequent and only occurred following V920. Pyrexia, headache, and arthralgia were the most commonly reported events between Day 1 to 42 and were more commonly reported after V920 and more commonly reported in the High Dose lot group compared to the consistency lot groups. The most commonly reported severe systemic events (>1% of subjects in any group) were exclusively reported after administration of V920, were generally reported more frequently in the High Dose group, and were events that are consistent with reactogenicity. Arthritis was reported exclusively after V920 and was reported by similar proportions of subjects in the Combined Lot group and the High Dose group. Rash was more commonly reported after V920 and was reported by similar proportions of subjects in the Combined Lot group and the High Dose group. RT-PCR for vaccine virus was positive in joint, vesicular rash, and skin biopsy specimens. None of the SAEs were considered related to V920 and no pattern of SAEs suggestive of a safety signal was identified.

6.4 Trial #4

V920-011: STRIVE (Sierra Leone Trial to Introduce a Vaccine against Ebola)
First subject first visit: April 9, 2015
Date of last subject visit: November 8, 2016
Sponsor name: Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services (HHS)

6.4.1 Objectives

Primary objectives:

- Estimate the efficacy of a single dose of the V920 vaccine in preventing laboratory-confirmed (study diagnostics) Ebola >21 days post-vaccination.
- Assess SAEs following administration of a single dose of the V920 vaccine.
- Collect and store serum for immunogenicity evaluations and assessment of baseline Ebola IgG antibody levels among a subset of study subjects.

Secondary objectives:

- Estimate the efficacy of a single dose of the V920 vaccine in preventing death due to laboratory-confirmed Ebola.

- Estimate the efficacy of a single dose of the V920 vaccine in preventing laboratory- confirmed Ebola at earlier time points post-vaccination (0 days, >7 days, >14 days).
- Estimate the efficacy of a single dose of the V920 vaccine in preventing 1) Ebola confirmed by non-study or study diagnostics, or 2) suspected, probable, or laboratory- confirmed Ebola.
- Assess reactogenicity and unsolicited AEs in a subgroup of approximately 400 subjects, including 200 subjects post-vaccination with a single dose of V920 vaccine, and 200 subjects who have not yet received vaccine (in the Deferred Vaccination arm).
- Monitor for an increase in risk of laboratory-confirmed Ebola following the V920 vaccine.

Reviewer's comment: Due to the waning Ebola epidemic at the time the study was conducted, no laboratory confirmed cases of EVD were observed in this study. Thus, only immunogenicity and safety objectives were assessed in the clinical study report.

6.4.2 Design Overview

STRIVE was an open-label, randomized study designed to evaluate the efficacy and safety of a single dose of V920 in a population of at-risk health care workers (HCW) and Ebola front-line workers. Eligible subjects were enrolled and individually randomized 1:1 to receive a single IM dose of V920 at a nominal dose of 2×10^7 pfu in an Immediate Vaccination group or a Deferred Vaccination group. Immediate vaccination was defined as vaccination within 7 days of enrollment, and deferred vaccination was defined as vaccination at the end of an 18 to 24-week follow-up period. After vaccination, members of the Deferred Vaccination group comprised the Crossover Vaccination group.

Subjects in each group completed a baseline questionnaire immediately prior to vaccination. Subjects in the delayed group underwent repeat eligibility screening to reconfirm eligibility prior to vaccination. Each subject received a thermometer and was instructed to contact study staff if they developed fever (≥38.0°C), clinical symptoms suggestive of EVD, or any other clinically significant medical event during the entire study period (though 6 months post-vaccination). Subjects were followed actively with monthly phone calls for EVD and evaluation of AEs. The study intended to compare events of laboratory-confirmed EVD between immediate and delayed vaccination within the 18 to 24-week post-vaccination time frame. All subjects were to be followed for 6 months after vaccination to monitor for SAEs.

A safety sub-study was planned to enroll 400 of the first subjects to be enrolled at the initial vaccination site (COMAHS Library). The safety sub-study collected solicited reactogenicity symptoms for the 28 days immediately following enrollment.

An immunogenicity sub-study included approximately 500 subjects who voluntarily enrolled from the Connaught Hospital site. Immunogenicity samples were collected from subjects at 1, 6, and 9 to 12 months. Due to concerns for potential transmission of Ebola virus, immunogenicity samples underwent gamma-irradiation (50 kilograys) prior to shipping.

Changes in study conduct:

- In August 2015, the WHO-led consortium conducting study V920-010 reported interim vaccine efficacy results which resulted in expansion of the ring study into Sierra Leone and the modification that all rings were to receive vaccine immediately. Enrollment in STRIVE was complete at this time; however, in response to a new Ebola outbreak and implementation of ring vaccination in one of the STRIVE enrollment districts, the STRIVE study protocol was amended in August 2015 to allow for early vaccination of deferred subjects who had been potentially exposed to Ebola (who may have been in contact with an Ebola case or worked in a health facility that treated an Ebola case).
- STRIVE was designed to be event-driven, and the study sample size was calculated based on an estimated maximum 67 observed Ebola infection events needed for the final efficacy analysis. However, as no EVD cases were observed during the study and the study laboratory was closed, assessments in the CSR were limited to safety and immunogenicity objectives, as stated above.

6.4.3 Population

Participation in the study was voluntary and open to healthy adults (and non-pregnant or not breastfeeding in the case of females) 18 years of age or older who were at high risk of exposure to Ebola infection through their work in the study districts. This included:

- personnel working in healthcare facilities where care was provided for Ebola patients;
- personnel working in non- Ebola healthcare facilities who may have been exposed to undiagnosed Ebola-infected individuals; and
- personnel working in one of the following front-line job categories: surveillance team, ambulance team, burial workers, or workers responsible for swabbing deceased persons.

Participation was limited to personnel who anticipated residing in Sierra Leone during an 18 to 24-week post-enrollment period (the follow-up time for the efficacy portion of the analysis). All subjects were required to be reachable by phone throughout the 6 months post-vaccination safety follow-up period. Subjects who had self-reported history of EVD or exposure to EVD, HIV, immunodeficiency, or allergy/anaphylaxis to prior vaccines; prior history of receipt of an experimental vaccine against Ebola or Marburg virus; receipt of experimental research agents within 28 days of vaccination; and/or had a fever of ≥38 ºC at the time of vaccination were excluded.

6.4.4 Study Treatments or Agents Mandated by the Protocol

The dose administered was $\geq 2 \times 10^7$ pfu/mL V920.

6.4.5 Directions for Use

Single dose of V920 or saline placebo administered IM into the deltoid.

6.4.6 Sites and Centers

A total of seven clinical sites enrolled subjects, including COMAHS library (22% of randomized subjects), Connaught Hospital (38% of randomized subjects), Magburaka Government Hospital (8% of randomized subjects), Saint John of God Kaffu Bullom (3% of randomized subjects), District Hospital (10% of randomized subjects), Saint John of God Nursing School Lunsar (5% of randomized subjects), and Holy Spirit Hospital (14% of randomized subjects).

6.4.7 Surveillance/Monitoring

Subjects were observed for 60 minutes following vaccination for immediate reactions. A monthly phone call was used to collect AE information for 6 months following vaccination. For subjects in the Immediate Vaccination group, the final monthly call occurred approximately 6 months from enrollment. For subjects in the Deferred Vaccination group, the final call occurred approximately 11 to 12 months from enrollment (18 to 24 weeks deferred vaccination time plus 6 months post-vaccination follow-up).

Subjects in the safety sub-study were provided with a diary card to record symptoms and received follow-up calls on Days 1, 3, 7, 14, and 28 to solicit local and systemic reactogenicity symptoms and to record unsolicited AEs and SAEs. Causality was assessed for Grade 3 and higher non-serious AEs and SAEs reported in the safety sub-study in the Day 0 to 28 time period.

Pregnancies that occurred within two months of enrollment or vaccination were followed to outcome. For pregnancies that results in a live birth, study personnel either reviewed delivery records (if infant delivered in or seen at a healthcare facility) or conducted a home visit to assess the infant. A follow up interview was conducted with the mother by phone on or after Day 28 of the infant's life.

This study was monitored by a DSMB.

6.4.8 Endpoints and Criteria for Study Success

The primary endpoint for evaluating the efficacy of V920 was laboratory-confirmed Ebola infection.

Safety endpoints included:

- SAEs and AEs from enrollment through 6 months after vaccination.
- Reactogenicity symptoms in the first 28 days after enrollment (safety sub-study), including local reactions (swelling, redness, and pain), fever/elevated temperature, feverishness, fatigue, feeling unwell, muscle pain, joint swelling, chills, headache, vomiting, nausea, diarrhea, abdominal pain, rash, oral ulcers, joint pain and skin vesicles (blisters).

The key immunogenicity endpoint was Ebola-specific antibodies over 12 months following vaccination with V920:

- 95% confidence intervals (CIs) of the GMTs and GMFRs from baseline for $PRNT_{60}$ and GP-ELISA
- Counts, percentages, and 95% CIs of the proportion of subjects who achieve seroresponse at any time post-vaccination and for each time point defined as:
    - GP-ELISA: Primary endpoint of a ≥2-fold increase in titers from baseline and ≥200 EU/mL and a secondary endpoint of a ≥4-fold increase in titers from baseline
    - PRNT: a ≥4-fold increase in titers from baseline

6.4.9 Statistical Considerations & Statistical Analysis Plan

<u>Sample size</u>

The trial was intended to be event-driven, with an estimated maximum 67 observed Ebola infection events needed for the final VE analysis. Calculation of the target number of enrolled participants was based on this maximum number of events. As no cases of EVD were observed during the study, an event-driven limit was not imposed on the study sample size.

Derived and transformed data

Safety data: Safety data are summarized according to time periods of interest:

- Overall population: From start to 6 months, from start to 1 month, from start to Month 2, Month 1 to 2, from start to 18 weeks, Month 2 to 18 weeks, and 18 weeks to 6 months. Subjects with no documented safety assessment in the time period of analyses are not included in the total number of subjects displayed in each group.
- Safety sub-study: Week 1 to 4, Week 1, Week 2, Week 3, Week 4

AEs were coded using MedDRA version 19.0.

Immunogenicity data: No imputation for missing data was performed. GP-ELISA values below the lower limit of quantification (LLOQ) were imputed to one-half the value of the LLOQ (i.e., 18.055 EU/mL).

For the assessment of humoral immunogenicity, the following applied:

- The 95% CI for the GMFRs and GMTs were based on analysis of variance and the 95% CI for seroresponse rate was based on the exact binomial method
- Subjects with a baseline GP-ELISA titer ≥200 EU/mL were considered seropositive at baseline.

Statistical analyses

Changes to the statistical plan included:

- Data listings by individual subject were not included per sponsor decision.
- Action taken as a result of a deviation was not collected on the source document or in the database.
- The planned efficacy analysis was removed from the SAP.
- A summary of the number of subjects excluded from each population is included in the final analyses, but demographics, baseline, and safety data were not described by these populations.
- History of joint pain was not collected in the source document or database.
- Safety events are not tabulated by resolution. All SAEs were followed to resolution.
- Data listings for all adverse events in the safety sub-study were not included.
- Only pregnancies occurring within two months of vaccination or enrollment were followed to completion.

The following analyses were added to the statistical plan:

- Fever, joint pain, joint swelling, rash, skin vesicles, and oral ulcers were summarized by percentage of subjects experiencing the symptom with any severity by time point, as well as by the number of reports, duration, and time of onset.
- Solicited systemic reactogenicity reported from Day 5 to 28 in the safety sub-study (events with an onset between Days 0 and 5 were excluded).

- Adverse events summarized by person-time, cumulatively, to account for differences in follow-up time between the Immediate and Delayed vaccination groups.

Time periods analyzed:

- Randomized Portion: The time period from enrollment and randomization of subjects until the beginning of intentional vaccination of subjects randomized to the Deferred Vaccination group.
- Crossover Vaccination Portion: The time period from the start of intentional vaccination of the subjects randomized to the Deferred Vaccination group through the end of the study.

Analysis populations

See Section 6.3.10.1 (Populations Enrolled/Analyzed) for information on the analysis populations.

Treatment group categories included:

- Immediate Vaccination: All subjects randomized to immediate vaccination, including both vaccinated and unvaccinated subjects as well as those whose vaccination occurred outside the window.
- Deferred Vaccination: All subjects randomized to deferred vaccination, including 12 subjects who were inadvertently vaccinated prior to crossover.
- Crossover Vaccination: All subjects randomized to deferred vaccination who intentionally received vaccination during the Crossover Period that began in September 2015 regardless of whether the vaccine was administered during the protocol specified 18 to 24-week post-enrollment window. Events are included in the Crossover Vaccination category if they occurred after vaccination.
- Post-Vaccination: Events that occur in vaccinated subjects.
- All Randomized: All subjects who were enrolled and randomized to either the Immediate or Deferred Vaccination groups. Data collected during the Randomized Portion and events that began during the Randomized Portion are included (i.e. does not include data after crossover vaccination).
- All Participants: The All Participants group includes every subject who was enrolled and randomized to either the Immediate or Deferred Vaccination groups. Data collected during both the Randomized Portion and the Crossover Portion, and events that begin during either portion, are included.
- Vaccinated: All subjects who were vaccinated during the Randomized Portion, including subjects randomized to either the Immediate or Deferred Vaccination groups.
- Unvaccinated: Subjects who were not vaccinated during the Randomized Portion of the trial, including subjects randomized to either the Immediate or Deferred Vaccination groups. For the safety sub-study, subjects who were vaccinated after the 28-day memory period are included in the Unvaccinated group for the safety sub-study tables. These subjects are included in the Vaccinated group for the overall safety summaries.
- All Vaccinated: All subjects who received vaccine, regardless of the randomization group assigned or time period in which vaccine was administered. Data collected during the study portion in which subjects were first vaccinated are included.

6.4.10 Study Population and Disposition

6.4.10.1 Populations Enrolled/Analyzed

The Full Analysis Set (FAS) population consisted of all randomized and vaccinated subjects in the immunogenicity subset with a serology assessment collected within the allowed time window specific to each endpoint (GP-ELISA and PRNT). The FAS population served as the primary population for the analysis of immunogenicity.

The Per Protocol (PP) population consisted of the FAS population for GP-ELISA and PRNT, excluding subjects with baseline GP-ELISA assay results ≥200 EU/mL, for violation of certain inclusion/exclusion criteria, and subjects with missing, unevaluable, or out-of-day-range serology result or sample at a particular time point.

The Full Study population for safety analyses included all randomized subjects who provided safety follow-up data during the 6-month follow-up period.

The safety sub-study Population included all subjects randomized to the safety sub-study who provided safety data.

6.4.10.1.1 Demographics

The following table summarizes the study population demographics by gender, race, nationality, site, and age by treatment group.

Table 41 Demographics

	Immediate Vaccination (N= 4319)	**Deferred Vaccination (N= 4332)**	**Deferred Vaccination Crossover (N= 3821)**	**All Vaccinated (N= 7998)**	**All Randomized (N= 8651)**
Female n (%)	1703 (39.4)	1704 (39.3)	1360 (35.6)	2954 (36.9)	3407 (39.3)
Male n (%)	2616 (60.5)	2628 (60.6)	2461 (64.4)	5044 (63.0)	5244 (60.6)
Asian n (%)	1 (<0.1)	2 (<0.1)	2 (<0.1)	3 (<0.1)	3 (<0.1)
Black n (%)	4316 (99.9)	4321 (99.9)	3811 (99.9)	7985 (99.9)	8637 (99.9)
White n (%)	0 (0)	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Multi-racial n (%)	2 (<0.1)	8 (0.1)	7 (0.1)	9 (0.1)	10 (0.1)
Kono	141 (3)	131 (3)	116 (3)	251 (3)	272 (3)
Krio	157 (4)	186 (4)	154 (4)	306 (4)	343 (4)
Limba	510 (12)	528 (12)	488 (13)	985 (12)	1038 (12)
Loko	155 (4)	165 (4)	150 (4)	300 (4)	320 (4)
Mandingo	217 (5)	199 (5)	171 (4)	379 (5)	416 (5)
Mende	691 (16)	772 (18)	651 (17)	1317 (16)	1463 (17)
Temne	1932 (45)	1826 (42)	1650 (43)	3527 (44)	3758 (43)
Susu	141 (3)	138 (3)	120 (3)	253 (3)	279 (3)
Sherbro	67 (2)	76 (2)	67 (2)	130 (2)	143 (2)
Fullah	156 (4)	164 (4)	132 (3)	283 (4)	320 (4)
Kuranko	66 (2)	69 (2)	60 (2)	123 (2)	135 (2)
Yalunka	18 (<1)	12 (<1)	10 (<1)	27 (<1)	30 (<1)
Yoruba	6 (<1)	3 (<1)	2 (<1)	7 (<1)	9 (<1)
Kissi	44 (1)	39 (1)	33 (1)	75 (1)	83 (1)
Unknown	1 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)
Other	17 (<1)	23 (1)	16 (<1)	33 (<1)	40 (<1)
Median age (years)	30.5	30.8	31.0	30.8	30.7

Source: Adapted from Original BLA 125690/1; Clinical Study Report V920-011, p.111, Table 10-9

Clinical sites with the highest enrollment included COMAHS library (22% of subjects in the Immediate and Delayed Vaccination arms) and Connaught Hospital (38% of subjects in the Immediate and Delayed Vaccination arms).

The demographics of the safety sub-study subjects were comparable between the treatment arms and comparable to the demographics of the study overall. In the Immediate Vaccination arm, 34% of subjects were female and the median age was 27.7 years. In the Deferred Vaccination arm, 33% of subjects were female and the median age was 27.4 years. In the immunogenicity sub-study, 42% of subjects were female and the median age was 32.1 years.

Reviewer's comment: Baseline demographic characteristics were comparable across the randomized treatment arms.

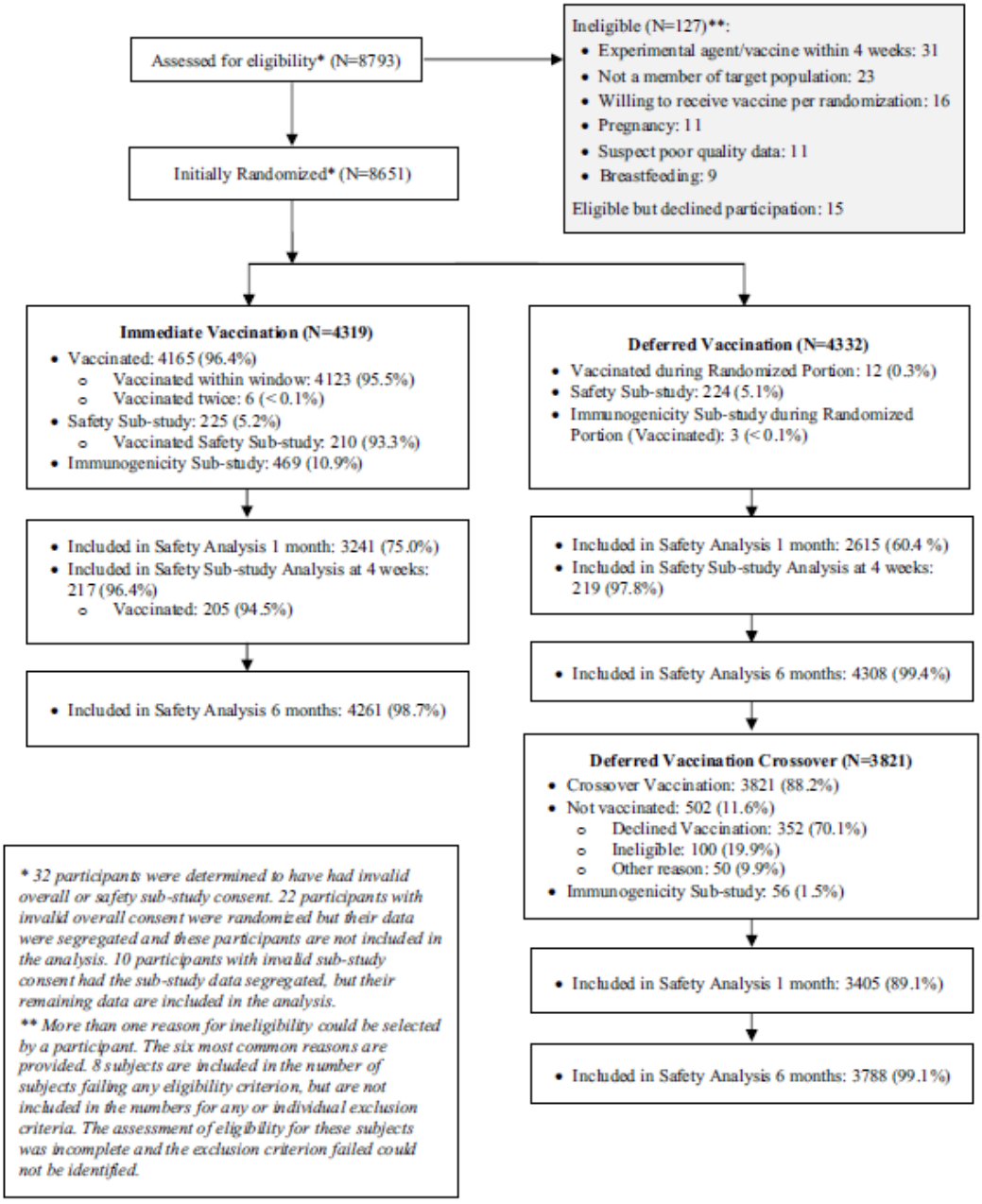
6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The proportions of subjects with specific baseline medical conditions were generally comparable between the treatment groups, although a higher proportion of subjects in the Immediate Vaccination group reported a baseline history of arthralgia (5.8%) compared to the Deferred Vaccination group (1.8%).

6.4.10.1.3 Subject Disposition

The following figure describes the enrollment and disposition of subjects:

Figure 1 Flow diagram of subject disposition



Source: Original BLA 125690/1; Clinical Study Report V920-011, p.193, Figure 10-1

The following table describes the reasons for early study withdrawal, by treatment group.

Table 42 Reasons for early study withdrawal by treatment group

Reason for early withdrawal	Immediate Vaccination (N= 4319) n (%)	Deferred Vaccination (N= 4332) n (%)	Deferred Vaccination Crossover (N= 3821) n (%)	All Randomized (N= 8651) n (%)	All Vaccinated (N= 7998) n (%)
Lost to follow up	152 (3.5)	32 (0.7)	181 (4.7)	184 (2.1)	327 (4.1)
Death	8 (0.2)	6 (0.1)	11 (0.3)	14 (0.2)	19 (0.2)
Withdrawal of consent	7 (0.2)	7 (0.2)	1 (<0.1)	14 (0.2)	4 (0.1)

Reason for early withdrawal	Immediate Vaccination (N= 4319) n (%)	Deferred Vaccination (N= 4332) n (%)	Deferred Vaccination Crossover (N= 3821) n (%)	All Randomized (N= 8651) n (%)	All Vaccinated (N= 7998) n (%)
Medical reason not related to the study	1 (<0.1)	3 (0.1)	0 (0)	4 (<0.1)	0 (0)
Not eligible for vaccination (Delayed group)	-	100 (2.3)	-	100 (1.2)	-
Declined vaccination (Delayed group)	-	352 (8.1)	-	352 (4.1)	-
Other	50 (1.2)	2 (<0.1)	0 (0)	52 (0.6)	0 (0)
Total	218 (5.0)	502 (11.6)	193 (5.1)	720 (8.3)	350 (4.4)

Source: Original BLA 125690/1; Clinical Study Report V920-011, p.94, Table 10-3

Reviewer's comment: Imbalances in study withdrawal between the Immediate and Deferred Vaccination groups included more subjects lost to follow up in the Immediate group (3.5%) compared to the Deferred group (0.7%) and more subjects declining vaccination in the Deferred group (8.1%) compared to the Immediate group (none). In the Immediate Vaccination group, the motivation to comply with follow-up may have been decreased after vaccination was received. In the Deferred Vaccination group, most subjects eventually declined vaccination, which was likely attributable to the waning epidemic.

FAS immunogenicity sub-study population Of the 528 subjects randomized for participation in the immunogenicity sub-study, 508 subjects were vaccinated and provided samples for the assessment of immunogenicity by GP-ELISA (n= 506) and PRNT (n= 504).

PP immunogenicity sub-study population The Per Protocol (PP) population consists of the FAS population for GP-ELISA (n= 424) and PRNT (n= 423), excluding subjects with baseline GP-ELISA assay results ≥200 EU/mL (n= 76 for GP-ELISA and n= 75 for PRNT), for violation of certain inclusion/exclusion criteria (n= 3 for GP-ELISA and PRNT), and subjects with missing, unevaluable, or out-of-day-range serology result or sample at a particular time point (at the Day 1, Month 1, Month 6, and Month 9-12 time points, n= 4, 64, 124, and 111, respectively, for GP-ELISA and n= 67, 68, 123, and 109, respectively for PRNT).

Full Study population for safety analyses Of the 8569 randomized subjects, 82 subjects did not provide any safety follow-up data during the 6-month follow-up period.

Safety sub-study Population Of the 449 participants enrolled in the safety sub-study, 436 provided safety sub-study follow up data and were included in analyses. Of the 225 subjects in the Immediate Vaccination group, 10 subjects were never vaccinated due to invalid study consent, and five participants were vaccinated only at the end of the 28-day follow-up period. The subjects vaccinated at the end of the follow-up period are included in safety analyses as unvaccinated subjects. The 10 subjects with invalid study consent and three additional subjects did not provide any safety data.

Compliance with safety data follow up

Safety sub-study population: In the safety sub-study, the percentage of subjects included in the safety analysis at 4 weeks was 94.5%. Information on compliance with filling out the diary card was not provided.

Full study population: Subjects who had their Month 1 assessment ≥31 days after start of follow-up and did not experience an AE or SAE, did not have reactogenicity data, or did not have an Ebola screening event during the first 30 days of follow-up were excluded from the Month 1 time period summaries. This policy resulted in the exclusion of 2795 subjects from the Month 1 summaries, including 1078 subjects in the Immediate Vaccination group (25.0%) and 1717 subjects in the Deferred Vaccination group (39.6%). These subjects were included in analyses of subsequent safety summaries.

During the 6-month safety follow-up period in the randomized portion of the study, safety data were not available at any time for 82 subjects, including 58 subjects in the Immediate Vaccination group (1.3%) and 24 subjects in the Deferred Vaccination group (0.6%). In the Deferred Vaccination Crossover group, 33 subjects (0.9%) did not provide any safety data in the 6-month post-vaccination follow up period.

Reviewer's comment: The number of subjects included in the 1-month safety analysis in both the Immediate and Deferred vaccination groups was low (75% and 60.4% of the total number of randomized subjects, respectively). As these subjects did not have AEs or SAEs, exclusion of these data would not be expected to result in an underestimation of rates of safety events. More aggressive follow-up attempts were incorporated into study procedures for the crossover period, resulting in the inclusion of 89.1% of subjects in the Deferred vaccination crossover group in the 1-month safety analysis.

Between 18 weeks and 6 months, 35.8% of subjects in the Deferred group did not provide safety data, compared to 5.9% of subjects in the Immediate Vaccination group.

Reviewer's comment: The Applicant attributes this imbalance to vaccination of Deferred Vaccination subjects between 18 and 24 weeks, at which time safety follow up was performed in the Deferred Vaccination Crossover group.

Protocol deviations: More subject-specific deviations were observed in the Immediate Vaccination group (1451 subjects / 2372 deviations) compared to the Deferred Vaccination (1002 subjects/ 1515 deviations) and Deferred-Crossover groups (1004 subjects/ 1853 deviations). Missed and out-of-window assessments comprised the majority of the deviations, including 1674 deviations in the Immediate Vaccination group, 1301 deviations in the Deferred Vaccination group, and 1757 deviations in the Deferred-Crossover group. The Applicant attributed this finding to the fact that the protocol defined the inability to reach a subject after 3 phone calls as a protocol deviation.

Other important protocol deviations included:

- Missed vaccination: In the Immediate Vaccination group, 154 subjects missed vaccination, including 144 subjects who refused vaccination, 3 subjects who were ill, 6 subjects who were unable to comply, and 1 subject with clinic error.
- Errors in consenting: Consenting irregularities included incorrect version signed, form not signed prior to study procedures, incomplete documentation of consent, no copy on consent given to subject, witness issues, and incorrect form used. All consent procedures were reviewed and all subjects with deviations were reconsented. Data from 32 subjects who were lost to follow-up and could not be

located for reconsent were excluded from the analysis. Additionally, there were multiple changes in translation procedures for the informed consent form due to concerns regarding understanding of written Krio, which is a non-codified language.

- Missed pregnancy testing: A total of 22 females under the age of 50 were enrolled without a documented negative pregnancy test. None of the women reported a pregnancy during the study period.
- Eligibility criteria violation: In addition to the 22 females without pregnancy testing, 18 subjects had deviations related to eligibility criteria. Other than a subject who reported a headache on the day of vaccination, no adverse events were documented for these subjects.
- Multiple enrollments/vaccination: A total of 29 subjects attempted to enroll multiple times at different study locations, most of whom were enrolled to the Deferred Vaccination group and continued to attempt to enroll until they were assigned to the Immediate Vaccination group. Six subjects were enrolled twice to the Immediate Vaccination group and received two vaccinations. Data for these subjects was consolidated, and all six double-vaccinated subjects were followed to 6 months after the second vaccination. No vaccine-related SAEs were reported by these subjects.
- Source documents missing: Certain source documents from 23 subjects could not be located after entry into the clinical and safety databases, and these data are considered not verified. However, these data were included in the study analyses with permission from the IRBs.
- Reporting of AEs/SAEs: It was determined that some follow-up phone calls had not been performed as specified and that there were documentation errors at the Port Loko site. After retraining, an improvement in site practices was noted. A data quality investigation was performed comparing data across follow-up sites including the time period prior to retraining, and a calculation of monthly SAE reporting rates indicated that SAE reporting was comparable to other study locations.

Non-subject-specific protocol deviations (n= 32) included errors in vaccine storage, study procedures that were done incorrectly or not performed, and other deviations.

Reviewer's comment: The sponsor determined that none of the protocol violations resulted in safety events encountered by subjects. Based on review of the CSR and associated appendices, their assessment appears accurate. In response to an IR, the sponsor indicated that it appeared a subject had been vaccinated during pregnancy (at 5 months). No additional information about this was available, and it was unclear if this was unrecognized previously.

6.4.11 Immunogenicity Analyses

A total of 508 subjects were included in the immunogenicity sub-study. The sub-study assessed IgG levels at baseline, and at 1 month, 6 months, and 9 to 12 months post-vaccination using the GP-ELISA and $PRNT_{60}$ assays. Samples were gamma-irradiated (50 kilograys) prior to shipping to inactivate any Ebola virus.

Reviewer's comment: See Section 6.2.11.1 (Analyses of Immunogenicity Endpoints) for a discussion of the impact of gamma-irradiation on samples.

6.4.11.1 Analyses of Primary and Secondary Endpoints

GP-ELISA
The following table summarizes the GMTs and GMFRs for GP-ELISA using the FAS at each time point.

Table 43 Summary of GP-ELISA geometric mean titer and geometric mean-fold rise (GP-ELISA FAS)

	Baseline (n)	**Month 1 (n)**	**Month 6 (n)**	**Month 9-12 (n)**
GMT [95%CI]	92.7 (503) [85.3, 100.9]	964.3 (443) [878.7, 1058.3]	751.8 (383) [690.6, 818.4]	760.8 (396) [697.6, 829.8]
GMFR [95%CI]	-	10.7 (441) [9.6, 12.0]	8.1 (381) [7.3, 9.1]	8.4 (393) [7.5, 9.4]

GMT= geometric mean titer; GMFR= geometric mean-fold rise
Source: Adapted from Original BLA 125690/1; Immunogenicity Statistical Report V920-011, p.25 and 27, Tables 4-4 and 4-5

Reviewer's comment: GP-ELISA titers peaked at the Month 1 time point, declined slightly at the Month 6 time point, and remained stable between Month 6 and Month 9-12. Immunogenicity appears to be greater for females at all time points and all subjects >50 years at later time points. GMTs were higher at all time points for baseline seropositive subjects; however, the GMFR was lower in this subgroup at all time points.

At baseline, 76 (15%) of 506 subjects tested were seropositive for GP-ELISA (defined as ≥200 EU/mL). Results from the GP-ELISA PP population, which excluded baseline seropositive subjects, were comparable to the FAS analysis, although numerically lower for GMT and numerically higher for GMFR at each time point.

To assess the impact of baseline seropositivity on GMTs and GMFRs, an analysis by baseline serostatus was conducted and is summarized in the following table.

Table 44 Summary of GP-ELISA geometric mean titer and geometric mean-fold rise by baseline serostatus (GP-ELISA FAS)

	Baseline (n)	**Month 1 (n)**	**Month 6 (n)**	**Month 9-12 (n)**
Baseline GP-ELISA ≥200 EU/mL GMT [95%CI]	543.3 (76) [439.1, 650.1]	1733.5 (63) [1359.6, 2210.3]	1305.5 (55) [1018.6, 1673.3]	1118.3 (57) [882.2, 1417.6]
Baseline GP-ELISA ≥200 GMFR [95%CI]	-	3.3 (63) [2.6, 4.3]	2.4 (55) [1.9, 3.1]	2.1 (57) [1.6, 2.6]
Baseline GP-ELISA <200 EU/mL GMT [95%CI]	67.9 (427) [64.4, 71.6]	880.4 (378) [798.4, 970.9]	686.8 (326) [629.6, 749.2]	713.4 (336) [650.3, 782.6]
Baseline GP-ELISA <200 GMFR [95%CI]	-	13.0 (378) [11.7, 14.6]	10.0 (326) [9.0, 11.1]	10.6 (336) [9.5, 11.9]

GMT= geometric mean titer; GMFR= geometric mean-fold rise
Source: Adapted from Original BLA 125690/1; Immunogenicity Statistical Report V920-011, p.25 and 27, Tables 4-4 and 4-5

Reviewer's comment: In the FAS, 15% of subjects had baseline GP-ELISA seropositive status, compared to 1% of subjects with baseline $PRNT_{60}$ seropositive status. The lack of a robust anamnestic response to V920 (GP-ELISA GMFR of 3.3 at Month 1 and 42.9% of baseline seropositive subjects with a 4-fold increase from baseline at any time) suggests either that the high rate of baseline seropositivity is due to assay variability or that V920 does not elicit a strong anamnestic response following wild-type Ebola exposure. Further, while the GMTs are higher at every time point for baseline seropositive subjects, the GMFR and seroresponse rates are lower compared to baseline seronegatives. It is unclear whether the muted responses relative to baseline in the seropositive subgroup is an artifact of the assay or interference from pre-existing antibodies.

Overall, seroresponse (2-fold increase from baseline and ≥200 EU/mL) rates were 94.1% at any time, 90% at Month 1, 89.5% at Month 6, and 87.8% at Month 9-12. Overall, seroresponse (4-fold increase from baseline) rates were 87.3% at any time, 79.8% at Month 1, 77.4% at Month 6, and 74.3% at Month 9-12.

Results from the GP-ELISA PP population were comparable to the FAS analysis, although the seroresponse rates were generally numerically higher at each time point. Consistent with the GMFR for baseline seropositive subjects described above, the seroresponse (4-fold increase from baseline) rate at any time point was 53.7% in baseline seropositive subjects compared to 92.9% in baseline seronegative subjects.

$PRNT_{60}$
The following table summarizes the geometric mean titers for PRNT (PRNT FAS).

Table 45 Summary of PRNT geometric mean titers overall and by age, gender, and baseline GP-ELISA (PRNT FAS)

	Baseline (n)	**Month 1 (n)**	**Month 6 (n)**	**Month 9-12 (n)**
GMT [95%CI]	<35 (438) [<35, <35]	116.0 (437) [105.7, 127.4]	95.3 (382) [86.3, 105.3]	119.9 (396) [107.9, 133.2]
GMFR [95%CI]	-	6.3 (376) [5.7, 7.0]	5.4 (326) [4.8, 6.0]	6.8 (342) [6.1, 7.6]

GMT= geometric mean titer; GMFR= geometric mean-fold rise
Source: Adapted from Original BLA 125690/1; Immunogenicity Statistical Report V920-011, p.34 and 36, Tables 4-8 and 4-9

Reviewer's comment: PRNT titers peaked at the Month 1 time point, declined slightly at the Month 6 time point, and remained stable between Month 6 and Month 9-12.

To assess the impact of baseline seropositivity on PRNT GMTs and GMFRs, an analysis by baseline GP-ELISA serostatus was conducted and is summarized in the following table.

Table 46 Summary of PRNT geometric mean titers geometric mean-fold rise by baseline GP-ELISA serostatus (PRNT FAS)

	Baseline (n)	**Month 1 (n)**	**Month 6 (n)**	**Month 9-12 (n)**
Baseline GP-ELISA ≥200 EU/mL GMT [95%CI]	<35 (63) [<35, <35]	128.5 (63) [96.2, 171.5]	83.5 (55) [609, 114.5]	94.3 (57) [68.4, 130.0]

	Baseline (n)	Month 1 (n)	Month 6 (n)	Month 9-12 (n)
Baseline GP-ELISA ≥200 GMFR [95%CI]	-	6.9 (52) [5.0, 9.3]	4.7 (44) [3.4, 6.5]	5.2 (46) [3.7, 7.4]
Baseline GP-ELISA <200 EU/mL GMT [95%CI]	<35 (374) [<35, <35]	114.1 (374) [103.4, 125.8]	97.7 (325) [88.0, 108.4]	125.8 (336) [112.6, 140.6]
Baseline GP-ELISA <200 GMFR [95%CI]	-	6.3 (324) [5.6, 6.9]	5.5 (281) [4.9, 6.2]	7.1 (295) [6.3, 8.1]

GMT= geometric mean titer; GMFR= geometric mean-fold rise, PRNT= plaque reduction neutralization test, FAS= full analysis set
Source: Adapted from Original BLA 125690/1; Immunogenicity Statistical Report V920-011, p.34 and 36, Tables 4-8 and 4-9

At baseline, 4 (1%) of 438 subjects tested had detectable PRNT, all of whom were also seropositive by GP-ELISA. Of the 4 subjects, 2 only had Day 1 immunogenicity data available. For the remaining 2 subjects, the PRNT GMFRs at Month 1, 6, and 9-12 were 1.9, 1.7, and 1.4 for the first subject and 7.4, 2.5, and 2.8 for the second subject, and the GP-ELISA GMFRs at Month 1, 6, and 9-12 were 1.0, 0.8, and 0.6 for the first subject and 4.8, 1.4, and 1.2 for the second subject.

Reviewer's comment: PRNT GMTs and GMFRs were generally comparable at each time point for subjects who were seropositive by GP-ELISA at baseline compared to those who were seronegative. Of the 2 subjects with baseline seropositivity by GP-ELISA and PRNT with full immunogenicity data available, one subject had minimal responses to vaccination; it is unclear whether this represents a true history of prior infection, assay variability, or the presence of a cross-reacting antigen.

Overall, seroresponse (4-fold increase from baseline) rates were 81.5% at any time, 70.5% at Month 1, 64.7% at Month 6, and 69.3% at Month 9 to 12. The seroresponse rate at any time point was 78.2% in baseline GP-ELISA seropositive subjects compared to 82.2% in baseline GP-ELISA seronegative subjects.

6.4.11.3 Subpopulation Analyses

The following table summarizes the GMTs for GP-ELISA by age and gender.

Table 47 Summary of GP-ELISA geometric mean titers overall and by age and gender (GP-ELISA FAS)

	Baseline (n)	Month 1 (n)	Month 6 (n)	Month 9-12 (n)
18-50 years GMT [95%CI]	93.4 (465) [85.6, 101.9]	963.7 (410) [875.8, 1060.4]	736.2 (353) [673.6, 804.6]	752.8 (364) [687.7, 824.1]
18-50 years GMFR [95%CI]	-	10.7 (408) [9.5, 12.0]	7.9 (351) [7.1, 8.9]	8.3 (361) [7.3, 9.4]
>50 years GMT [95%CI]	85.2 (38) [61.5, 117.9]	971.9 (33) [649.0, 1455.3]	962.2 (30) [720.3, 1285.4]	858.1 (32) [623.2, 1181.6]
>50 years GMFR [95%CI]	-	10.9 (33) [7.0, 17.0]	10.9 (30) [7.1, 16.7]	9.5 (32) [6.2, 14.6]
Female GMT [95%CI]	76.8 (211) [67.6, 87.2]	1057.9 (183) [907.8, 1232.7]	904.9 (162) [787.1, 1040.4]	972.9 (171) [849.3, 1114.4]
Female GMFR [95%CI]	-	14.5 (181) [12.0, 17.4]	11.6 (161) [9.8, 13.7]	13.0 (169) [10.8, 15.6]

	Baseline (n)	Month 1 (n)	Month 6 (n)	Month 9-12 (n)
Male GMT [95%CI]	106.3 (292) [95.3, 118.6]	903.4 (260) [804.1, 1015.0)	655.3 (220) [591.2, 726.4]	631.2 (225) [567.1, 702.5]
Male GMFR [95%CI]	-	8.7 (260) [7.6, 10.0]	6.3 (220) [5.5, 7.2]	6.0 (224) [5.2, 6.9]

GMT= geometric mean titer; GMFR= geometric mean-fold rise
Source: Adapted from Original BLA 125690/1; Immunogenicity Statistical Report V920-011, p.25 and 27, Tables 4-4 and 4-5

At each time point, seroresponse (2-fold increase from baseline and ≥200 EU/mL) rates were highest for females and subjects >55 years of age. At each time point, seroresponse (4-fold increase from baseline) rates were highest for females and subjects 18 to 50 years of age.

Reviewer's comment: In general, GP-ELISA titers were higher for females and older subjects, although antibody responses in males and younger subjects were present, with GMFR ≥6.0 at each time point.

The following table summarizes the geometric mean titers for PRNT by age and gender.

Table 48 Summary of PRNT geometric mean titers overall and by age, gender, and baseline GP-ELISA (PRNT FAS)

	Baseline (n)	Month 1 (n)	Month 6 (n)	Month 9-12 (n)
18-50 years GMT [95%CI]	< 35 (404) [<35, <35]	116.7 (404) [105.9, 128.5]	93.4 (352) [84.2, 103.5]	119.6 (364) [107.3, 133.4]
18-50 years GMFR [95%CI]	-	6.4 (346) [5.7, 7.0]	5.3 (299) [4.7, 5.9]	6.8 (313) [6.1, 7.7]
>50 years GMT [95%CI]	< 35 (34) [<35, <35]	108.6 (33) [74.9, 157.5]	121.6 (30) [81.8, 180.8]	123.0 (32) [79.4, 190.6]
>50 years GMFR [95%CI]	-	6.1 (30) [4.1, 9.2]	6.9 (27) [4.4, 10.7]	6.9 (29) [4.2, 11.1]
Female GMT [95%CI]	< 35 (183) [<35, <35]	135.8 (179) [117.0, 157.7]	134.4 (162) [115.5, 156.3]	176.3 (171) [150.3, 206.9]
Female GMFR [95%CI]	-	7.0 (151) [6.1, 8.2]	7.3 (137) [6.2, 8.6]	10.1 (148) [8.5, 12.0]
Male GMT [95%CI]	< 35 (255) [<35, <35]	104.0 (258) [92.4, 117.1]	74.0 (220) [65.4, 83.8]	89.4 (225) [78.7, 101.7]
Male GMFR [95%CI]	-	5.9 (225) [5.2, 6.7]	4.3 (189) [3.8, 4.9]	5.0 (194) [4.4, 5.8]

GMT= geometric mean titer; GMFR= geometric mean-fold rise,
Source: Adapted from Original BLA 125690/1; Immunogenicity Statistical Report V920-011, p.34 and 36, Tables 4-8 and 4-9

Seroresponse rates (4-fold increase from baseline) by gender and age reflected the GMT and GMFR data above, with a higher seroresponse rate observed in females.

Reviewer's comment: PRNT titers were higher for females, but comparable across the age groups.

6.4.11.4 Dropouts and/or Discontinuations
Please see Section 6.4.10.1.3 (Subject Disposition) for a description of subjects excluded from the immunogenicity analysis.

6.4.12 Safety Analyses

6.4.12.1 Methods

Solicited reactogenicity data are presented for vaccinated subjects in the safety sub-study for the first 28 days after enrollment, including fever/elevated temperature, feverishness, fatigue, feeling unwell, muscle pain, joint swelling, chills, headache, vomiting, nausea, diarrhea, abdominal pain, rash, oral ulcers, joint pain and skin vesicles (blisters). Local reactogenicity data was only collected from vaccinated subjects. Of the 215 vaccinated subjects, safety data for 210 subjects were available for the Week 1 visit, and safety data for 205 subjects were available for the Week 4 visit.

SAEs and AEs from enrollment through 6 months after vaccination are presented for all randomized subjects by treatment group and by vaccination status.

6.4.12.2 Overview of Adverse Events

Safety sub-study
Solicited local adverse events
Solicited local adverse events were only collected for vaccinated safety sub-study subjects in the Immediate Vaccination group. Of the 210 vaccinated subjects with safety data through Day 7, injection site pain, redness, and swelling were reported by 79.0%, 1.0%, and 2.9% of subjects, respectively. Most of the events were mild, none of the events were severe, and most subjects reported the events between Days 0 and 4 after vaccination. Between Days 8 and 28, only 6 subjects reported solicited local adverse events, all of which were pain. Of the 205 vaccinated subjects with data through Week 4, 164 (80%) reported any local solicited event.

Reviewer's comment: In response to an IR, the Applicant clarified the denominators for the safety database to specify that 210 subjects had safety data available through Week 1 after vaccination and 205 subjects had safety data available through Week 4.

Solicited systemic adverse events
In the 28-day period following vaccination, any solicited systemic event was reported by a higher proportion of vaccinated subjects (91.7% overall and 3.9% severe) compared to unvaccinated subjects (53.7% overall and 0.9% severe). Headache, feverishness, and fatigue were the most commonly reported systemic events. The majority of severe events were elevated temperature occurring within 7 days of vaccination. The proportions of subjects reporting any solicited systemic event was highest in the first 7 days following vaccination (91.2% of vaccinated subjects and 35.5% of unvaccinated subjects); in the Day 15-28 time period, the proportions of subjects reporting any solicited systemic event were lower (34.3% of vaccinated subjects and 19.4% of unvaccinated subjects).

The following table summarizes the proportions of subjects reporting solicited systemic adverse events in each treatment group for the 28 day follow up period.

Table 49 Solicited systemic reactogenicity through Day 28 by symptom and vaccination status

	Vaccinated N= 205 n (%)	Unvaccinated (N= 231) n (%)
Headache	156 (76.1)	78 (33.8)
Feverishness	109 (53.2)	33 (14.3)
Fatigue	108 (52.7)	34 (14.7)
Joint pain	79 (38.5)	21 (9.1)
Feeling unwell	66 (32.2)	18 (7.8)
Muscle pain	66 (32.2)	16 (6.9)
Fever/elevated temperature	49 (23.9)	22 (9.5)
Chills	39 (19.0)	14 (6.1)
Abdominal pain	37 (18.0)	16 (6.9)
Rash	24 (11.7)	5 (2.2)
Nausea	12 (5.9)	3 (1.3)
Diarrhea	10 (4.9)	3 (1.3)
Skin vesicles	9 (4.4)	2 (0.9)
Joint swelling	7 (3.4)	2 (0.9)
Oral ulcers	7 (3.4)	3 (1.3)
Vomiting	5 (2.4)	3 (1.3)

Source: Adapted from original BLA 125690/2; Clinical Study Report V920-011, p.464, Table 14-53

Severe events after vaccination included fever (n=5; 2.4%) and fatigue, joint pain, headache, diarrhea, and abdominal pain (n= 1 each; 0.5%). Severe events reported by unvaccinated subjects included fever (n= 2; 0.9%).

Reviewer's comment: Every solicited systemic adverse event was reported more frequently in the Immediate Vaccination group compared to the Deferred Vaccination group, although, interpretation of this safety data is confounded by the open-label study design. Severe solicited systemic events were observed following V920, the majority of which were fevers occurring within seven days of vaccination.

Subanalyses of the following adverse events of special interest were conducted for the safety sub-study (Day 0-28) comparing vaccinated to unvaccinated subjects.

Joint pain/swelling

Events of joint pain were reported by a higher proportion of vaccinated subjects (39%) than unvaccinated subjects (9.1%), including one vaccinated subject with a severe event of joint pain reported between Days 15 to 21. Events of joint pain were most frequently reported Days 0 to 7. Events reported in the vaccinated subjects occurred sooner, with a median time to onset of initial symptoms of 1 day (range, 0 – 26 days) for vaccinated subjects and 4 days (range, 0-5 days) for unvaccinated subjects, and lasted longer, with a median duration of 3 days (range, 1-21 days) for vaccinated subjects and 2 days (range, 2-6 days) for unvaccinated subjects. At Day 28, a total of eight vaccinated subjects reported ongoing events of joint pain. A severe event of joint pain was reported by a subject in the Immediate Vaccination group; however, this report was confounded by concomitant malaria.

Events of joint swelling were also reported by a higher proportion of vaccinated subjects (3.4%) than unvaccinated subjects (0.9%), none of which were severe and most of which were reported Days 0 to 7. The median time to initial onset and duration were 2 days for both vaccinated and unvaccinated subjects.

Rash/Vesicular rash
Events of rash were reported by a higher proportion of vaccinated subjects (12%) than unvaccinated subjects (2.2%), none of which were severe and most of which were reported Days 0-14. In vaccinated subjects, the median time to initial onset was 7 days with a median duration of 4 days, while unvaccinated subjects had a longer median time to initial onset (15 days) and shorter median duration (2 days). At Day 28, a total of six events (5 in the vaccinated group and one in the unvaccinated group) were ongoing.

Events of vesicular rash were also reported by a higher proportion of vaccinated subjects (4.4%) than unvaccinated subjects (0.9%), none of which were severe and most of which were reported Days 0 to 7. The median time to initial onset and duration were 2 days for both vaccinated and unvaccinated subjects. In vaccinated subjects, the median time to initial onset was 1 day, compared to 24 days in unvaccinated subjects. The median duration was comparable (3 days in both groups), although the mean duration was longer in vaccinated subjects (6.5 days), compared to 3 days in unvaccinated subjects. At Day 28, a total of two events in the vaccinated group were ongoing.

Oral ulcers
The proportion of subjects reporting oral ulcers was slightly higher in vaccinated subjects in the Days 0 to 7 and 8 to 14 time periods (1.5% and 2%, respectively) compared to unvaccinated subjects (0.4% and 0%, respectively), but was generally comparable in the Day 15-28 time period. No events were severe, and the median duration of events was 3 days for vaccinated subjects.

Fever
Events of fever (temperature ≥38.0°C) were reported by a higher proportion of vaccinated subjects (24%) than unvaccinated subjects (9.6%). Severe events of fever were reported by 2.4% of vaccinated subjects and 0.9% of unvaccinated subjects. Events were most frequently reported in the Day 0 to 7 time period, with a median time to initial onset of 1 day in vaccinated subjects and 9 days in unvaccinated subjects. The duration of fever was the same in both groups (2 days). Multiple events of fever were reported for subjects in both groups, with a total of 72 events of fever reported in 49 vaccinated subjects and 36 events of fever in 22 unvaccinated subjects.

Unsolicited events
Unsolicited events were reported by a higher proportion of all vaccinated subjects in the Immediate Vaccination group (49.3%, including 4.4% of subjects with severe events) compared to unvaccinated subjects the Deferred Vaccination group (11.7%, including 1.3% of subjects with severe events) in the Day 0 to 28 time period. The difference between the groups was most pronounced in the first week following vaccination, during which 39.5% of vaccinated subjects in the Immediate Vaccination group reported unsolicited events compared to 3.9% of unvaccinated subjects in the Deferred Vaccination group.

The following table summarizes unsolicited events reported by a higher proportion of vaccinated subjects compared to unvaccinated subjects and by more than two subjects.

Table 50 Unsolicited events reported by a higher proportion of vaccinated subjects compared to unvaccinated subjects and by 2 or more subjects (Safety sub-study population)

MedDRA Preferred Term	Vaccinated (N= 205) n (%)	Unvaccinated (N= 231) n (%)
Pain	14 (6.8)	4 (1.7)
Asthenia	12 (5.9)	2 (0.9)
Back pain	10 (4.9)	0 (0)
Pruritis	8 (3.9)	0 (0)
Chest pain	6 (2.9)	5 (2.2)
Pyrexia	6 (2.9)	2 (0.9)
Furuncle	6 (2.9)	0 (0)
Pain in extremity	6 (2.9)	0 (0)
Dizziness	6 (2.9)	1 (0.4)
Pruritis generalized	6 (2.9)	2 (0.9)
Decreased appetite	5 (2.4)	0 (0)
Nasopharyngitis	4 (2.0)	2 (0.9)
Flank pain	5 (2.4)	0 (0)
Limb discomfort	5 (2.4)	0 (0)
Malaria	3 (1.5)	1 (0.4)
Headache	3 (1.5)	0 (0)
Amenorrhea	3 (1.5)	0 (0)
Increased appetite	3 (1.5)	0 (0)
Palpitations	2 (1.0)	0 (0)
Eye pain	2 (1.0)	1 (0.4)
Abdominal pain	2 (1.0)	1 (0.4)
Wound	2 (1.0)	0 (0)
Muscle spasms	2 (1.0)	0 (0)
Neck pain	2 (1.0)	0 (0)
Menorrhagia	2 (1.0)	0 (0)
Vaginal discharge	2 (1.0)	0 (0)
Hyperhidrosis	2 (1.0)	0 (0)
Night sweats	2 (1.0)	0 (0)

Source: Adapted from Original BLA 125690/43; Response to Information Request, p. 41-46, Table 4-1

Severe events reported after vaccination included pyrexia (n= 5; 2.4%), malaria (n= 1; 0.5%), and headache (n= 1; 0.5%). Severe events reported by unvaccinated subjects included pyrexia and malaria (n= 1 each; 0.4%).

Reviewer's comment: In response to an IR, the Applicant provided tabular summaries of unsolicited events by vaccination status through Week 4 for the safety subset population. Causality was not assessed for unsolicited events in the safety subset; however, a pattern of events of increased events of pain (both localized and general) and asthenia in the vaccinated group was noted which is suggestive of vaccine reactogenicity. An imbalance in severe events was also noted, most of which were fever, also suggesting that vaccine reactogenicity manifested with severe symptoms. Overall, the proportions of subjects reporting any single MedDRA PT was low and severe events other than pyrexia were uncommon.

Full safety population

Reviewer's comment: In the CSR for study V920-011 (reviewed below), the analyses of unsolicited events were provided by treatment group, including a group "post-

vaccination," which included the 7960 vaccinated subjects with safety data available. However, there was no comparison of vaccinated and unvaccinated subjects for the randomized portion of the study. In response to an IR, the Applicant provided tabular summaries of unsolicited events by vaccination status in the randomized portion of the study through Month 6 for the full safety population. The Applicant stated that the CSR and SAP performed the safety analysis of unsolicited events for the full safety population using a modified intention to treat analysis (i.e. by treatment group as opposed to vaccination status) due to a concern that an "as treated" approach would introduce significant bias due to differential follow-up and reporting as the study was open-label. Due to this reviewer's concern that the inclusion of unvaccinated subjects in the Immediate Vaccination group may result in an underestimation of the proportions of exposed subjects reporting events, the analysis in this review includes an assessment of safety based on vaccination status during the randomized portion of the study (i.e., the data excludes subjects vaccinated in the Deferred-Crossover group). To assess unsolicited events reported by all vaccinated subjects, the proportions of subjects reporting events post-vaccination, including subjects vaccinated in the Deferred-Crossover group, are summarized. There is no comparator group for this assessment. The safety analysis for the Month 1 time period includes only those subjects who had safety data available (as described above).

Overall, during the randomized portion of the study, unsolicited events were reported by 59.8% of vaccinated subjects compared to 12.5% of unvaccinated subjects through Month 1. The following table summarizes non-serious unsolicited events reported by a higher proportion of vaccinated subjects compared to unvaccinated subjects and by ≥5% of subjects through Month 1, during the randomized portion of the study.

Table 51 Non-serious unsolicited events reported by a higher proportion of vaccinated subjects compared to unvaccinated subjects and by more than ≥5% subjects through Month 1 (Full safety population; randomized portion of study)

MedDRA Preferred Term	Vaccinated (N= 3198) n (%)	Unvaccinated (N= 2658) n (%)
Headache	978 (30.6)	122 (4.6)
Pain	392 (12.3)	71 (2.7)
Pyrexia	315 (9.8)	35 (1.3)
Arthralgia	301 (9.4)	24 (0.9)
Asthenia	272 (8.5)	18 (0.7)
Feeling hot	219 (6.8)	18 (0.7)
Decreased appetite	170 (5.3)	25 (0.9)
Fatigue	161 (5.0)	21 (0.8)

Source: Adapted from Original BLA 125690/43; Response to Information Request, p. 68-82, Table 4-3

Severe events after vaccination included pyrexia (n= 17; 0.5%), headache (n= 2; 0.1%), and fatigue and feeling hot (n= 1 each; <0.1%). Severe events reported by unvaccinated subjects included pyrexia (n=2; 0.1%).

Reviewer's comment: Due to the large numbers of infrequently reported non-serious unsolicited events, a threshold of ≥5% of subjects reporting any event was used to focus on the most commonly reported events. Events of interest that were reported by <5% of subjects after vaccination are described below.

Overall, during the randomized portion of the study, unsolicited events were reported by 60.3% of vaccinated subjects compared to 23.1% of unvaccinated subjects through Month 6. The following table summarizes non-serious unsolicited events reported by a higher proportion of vaccinated subjects compared to unvaccinated subjects and by ≥5% of subjects through Month 6, during the randomized portion of the study.

Table 52 Non-serious unsolicited events reported by a higher proportion of vaccinated subjects compared to unvaccinated subjects and by ≥5% subjects through Month 6 (Full safety population; randomized portion of study)

MedDRA Preferred Term	Vaccinated (N= 4172) n (%)	Unvaccinated (N= 4397) n (%)
Headache	1408 (33.7)	45 (10.1)
Pain	664 (15.9)	265 (6.0)
Arthralgia	528 (12.7)	144 (3.3)
Pyrexia	468 (11.2)	135 (3.1)
Feeling hot	405 (9.7)	122 (2.8)
Asthenia	364 (8.7)	79 (1.8)
Decreased appetite	356 (8.5)	141 (3.2)
Abdominal pain	242 (5.8)	139 (3.2)
Fatigue	239 (5.7)	63 (1.4)
Nasopharyngitis	233 (5.6)	114 (2.6)

Source: Adapted from Original BLA 125690/43; Response to Information Request, p. 48-67, Table 4-2

Severe events after vaccination included pyrexia (n= 28; 0.7%); abdominal pain and headache (n= 2 each; 0.1%); arthralgia, fatigue, pain and feeling hot (n= 1 each; <0.1%). Severe events reported by unvaccinated subjects included pyrexia (n=8; 0.2%) and headache (n= 1; <0.1%).

Overall, any mild, moderate, and severe unsolicited event was reported by 46.5%, 3.2%, and 0.7% of all vaccinated subjects (n= 7960 including the Deferred-Crossover group).

Reviewer's comment: Unsolicited events were reported by a smaller proportion of subjects in the Deferred-Crossover group compared to the Immediate Vaccination group in the 6-month post-vaccination period and the pattern of the most commonly reported events was similar between the groups.

Non-serious unsolicited events of interest included arthralgia/arthritis, vision changes, and neurologic events.

- In the full safety population, the proportion of subjects reporting arthralgia post-vaccination, irrespective of treatment group, was 11.2% mild, 0.1% moderate, and <0.1% severe, compared to 3.3% of subjects in the Deferred Vaccination group reporting mild events. The proportion of subjects reporting joint swelling were comparable post-vaccination (0.2% of subjects, all mild events) and in the Deferred Vaccination group (0.1%, all mild events).

- Post-vaccination, 39 subjects (0.5%) reported events of vision blurred, visual acuity reduced, visual impairment, or blindness. The event of blindness was reported by a subject in the Immediate Vaccination group with a verbatim term of "unable to see", was mild and occurred 124 days after vaccination. All events were mild, with the exception of two moderate events of blurred vision, each

reported >100 days after vaccination. A total of five subjects in the Deferred Vaccination group reported blurred vision (0.1%).

- Post-vaccination, events of abasia and monoparesis were reported by two subjects each. Both events of monoparesis were mild, with verbatim terms of "weakness in the legs" and weakness of the left leg" and times to onset of 128 days and 30 days after vaccination, respectively. Both events of abasia were reported with the verbatim term of "unable to walk," one event of which was mild and reported 10 days after vaccination with a 2 day duration, and one event of which was severe and reported 166 days after vaccination (no duration provided) along with an event of communication disorder ("unable to talk").

Reviewer's comment: A full interpretation of safety data is limited by bias introduced due to the open-label study design, differential reporting periods between vaccinated and unvaccinated subjects, and a lack of comparator group for subjects vaccinated outside the randomized portion of the study (Deferred-Crossover group). Additional details regarding non-serious events of vision changes, abasia, and monoparesis are not available. However, these events were generally reported as mild, with moderate and severe events occurring temporally distant from vaccination (>100 days).

In general, the most frequently reported adverse events after vaccination in the full safety population are consistent with the findings in the safety subset.

6.4.12.3 Deaths

During the 6-month follow-up period, eight subjects (0.2%) in the Immediate Vaccination group, 11 subjects (0.3%) in the Deferred-Crossover group (SAE reported in Deferred Vaccination group, death occurred during Deferred-Crossover period), and five subjects (0.1%) in the Deferred Vaccination group died. An additional subject (Deferred Vaccination group) who did not receive V920 died during post-6 month follow-up. None of the deaths were attributed to vaccination.

Fatal events reported by subjects in the Immediate Vaccination group included loss of consciousness, encephalitis, HIV wasting syndrome, electrocution, acute abdomen, pancreatitis, subarachnoid hemorrhage, and malaria. All of the fatal events had a time to onset of >60 days after vaccination. Fatal events reported by subjects in the Deferred-Crossover group included malaria, drowning, spinal cord injury, cerebrovascular accident, myocardial infarction, hepatic cirrhosis, death, skeletal injury, pyonephrosis, and hemorrhagic stroke. Of these events, two occurred within 30 days of vaccination, including skeletal injury due to a road traffic accident and death due to an unknown cause 10 days after vaccination (described below in detail). Fatal events reported by subjects in the Deferred Vaccination group included pulmonary tuberculosis, nasopharyngeal cancer (death occurred after crossover to Deferred Vaccination group), sickle cell anemia with crisis, peptic ulcer perforation, hepatocellular carcinoma, and renal failure. Available details for fatal events reported after V920 are provided below.

Fatal cerebrovascular events were reported for three subjects after V920, including:

- A 52-year old female in the Deferred-Crossover group reported a fatal event of cerebrovascular accident. On Day 56 after vaccination, the subject experienced right hemiplegia and aphasia. She was admitted to an intensive care unit 5 days after the onset of symptoms. Prior to her death on Day 67, she experienced fever

for 3 days, night sweats, breathing problems and wheezing, severe headache, and loss of consciousness.

- A 57-year old male in the Deferred Vaccination group with a history of diabetes and hypertension, including a previous episode of hypertensive crisis, reported a fatal event of acute hemorrhagic stroke. On Day 73 after V920, the subject had hypertension (200/80 mmHg), loss of consciousness, and hyperglycemia (234 mg/dL). A diagnosis of acute hemorrhagic stroke was made (no radiologic test results were reported). On the day after admission, the subject remained unconscious with elevated glucose and coffee ground gastric contents and his blood pressure declined to 160/80mmHg. Despite multiple medical interventions, the subject died on Day 74. Malaria testing was positive, although he had no clinical malaria symptoms.
- A 53-year old female in the Immediate Vaccination group with a history of hypertension reported a fatal event of subarachnoid hemorrhage. The subject had a severe headache on Day 145 and died 3 days later. She was not hospitalized prior to her death. She was diagnosed with subarachnoid hemorrhage, although it is not clear how this diagnosis was made.

Reviewer's comment: Including the fatal events of hemorrhagic stroke and cerebrovascular accident, an additional non-fatal serious neurovascular event was reported by a 39-year old female with a history of hypertension who presented with slurred speech and right sided weakness 77 days after V920 and was diagnosed with cerebrovascular accident. Neurovascular events were only reported after V920, although it is difficult to compare frequencies due to the open-label design of the study. The time to onset of neurovascular events after vaccination was >50 days for all reports. Please see Section 8.4.8 (Adverse Events of Special Interest) for additional details.

Events reported after V920 without a clear etiology for the fatal outcome included the following:

- A 22-year old male enrolled in the Deferred-Crossover group with a history of peptic ulcer disease was reported to have experienced a fatal event with an unknown cause of death. Per a history provided by the subject's brother, the subject had a 6-month history of feeling unwell with abdominal (severe for 3 months) and back pain. On Day 10 after vaccination, the subject reported severe abdominal pain, loss of appetite, fatigue, weakness, joint pain, muscle pain, fast breathing, and headache. Upon admission to the hospital, he was afebrile and alert but lethargic. He was diagnosed with gastroenteritis and treated with fluids, antibiotics and other medications. Testing for malaria and typhoid fever was reportedly negative. His relative elected to take him home against medical advice on the second day of hospitalization. He died of an unknown cause 8 days after the onset of symptoms and 18 days after vaccination.

Reviewer's comment: This report describes symptoms that have been commonly observed following V920, including abdominal pain, fatigue, myalgia, arthralgia and headache, and is temporally related to vaccination. Confounding factors include a prolonged history of severe abdominal pain prior to vaccination. In the absence of any diagnostic information, the relevance of pre-existing condition or the recent vaccination is unclear. A full causality assessment of this report is precluded by a lack of data regarding events leading to the fatal outcome, a diagnosis for the symptoms preceding

vaccination, and the lack of any medical interventions in the days immediately preceding his death.

- A 24-year old healthy male hygienist at a regional Ebola Treatment Unit enrolled in the Immediate Vaccination group was reported to have experienced a fatal event of loss of consciousness on Day 62. He had the sudden onset of chills followed by difficulty in locomotion and breathing which led to collapse 62 days after vaccination. Other reported symptoms included visual hallucinations, vomiting, and loose stools. He was transported to the hospital where he was found to be unconscious and afebrile. A history of nausea, diarrhea, unexplained bleeding, and bloody stool was reported on the Ebola screening. He was treated with ceftriaxone and Ringer's lactate. He failed to regain consciousness, had hematemesis once, and died 7 hours after becoming ill and being taken to the hospital. Two postmortem swabs for Ebola were negative. The cause of death is unknown and additional diagnostic information is not available.

- A 29-year old healthy male enrolled in the Immediate Vaccination group was reported to have experienced a fatal event of encephalitis. The subject had the sudden onset of chills Day 178 after vaccination. He became unconscious and was transported to a non-study hospital later that same day where he regained consciousness within 30 minutes after receiving Ringer's lactate and artemether antimalarial treatment, but was confused, shouting deliriously, and hallucinating. He was later taken against medical advice by a relative to an herbalist who gave him native herb concoction. He died at home the following day. This report was assigned a PT of encephalitis at the discretion of the PI. Additional diagnostic information is not available.

Reviewer's comment: The above two cases are characterized by the sudden onset of loss of consciousness and hallucinations in young healthy males who die shortly after the onset of symptoms. Both events are temporally distant from vaccination (62 and 178 days, respectively), at a time when vaccine viremia would no longer be expected, and could have alternative toxicologic or infectious etiologies, although there is no or limited diagnostic data provided in case narratives. Similar cases were not observed in other studies.

- A 52-year old male enrolled in the Immediate Vaccination group was reported to have experienced a fatal event of acute abdomen. The subject was admitted to the hospital with a 3-day history of fever, vomiting, severe abdominal pain, distention, and constipation Day 85 after vaccination and died the day of admission with a suspected bowel obstruction.

- A 27-year old male enrolled in the Immediate Vaccination group was reported to have experienced a fatal event of pancreatitis. On Day 87, the subject reported epigastric pain, heartburn, vomiting, and weakness and was admitted to the hospital on Day 90. He had a positive hepatitis B surface antigen test. He remained hospitalized through Day 101, at which time he was weak, hypotensive, and complained of constipation. He died on Day 101 of an unclear cause.

Reviewer's comment: The above two cases are similar with respect to timing and an apparent abdominal origin of symptoms, although there is limited diagnostic data to support the provided diagnoses and no obvious biologically plausible mechanism to support a relationship to V920.

- A 50-year old male in the Deferred-Crossover group with a history of poorly-controlled diabetes mellitus and hypertension was reported to have experienced a fatal event of myocardial infarction on Day 135 after V920. On Day 135 she reported headache and chest tightness and was admitted to the hospital the following day, at which time she was "barely conscious." She had profuse vomiting and was not eating. The physician assessed her case as a possible state of dehydration worsened by hypoglycemia and further compounded by hyperkalemia. On the day of admission to the hospital, the subject died and severe dehydration or myocardial infarction were regarded as possible causes of death.

Reviewer's comment: Multiple factors (pre-existing diabetes, acute dehydration, temporal distance from vaccination) do not suggest a causal relationship to V920.

- A 35-year old in the Deferred-Crossover group was reported to have experienced a fatal event of liver cirrhosis on Day 99 after V920. On Day 89, the subject reported the onset of mild abdominal pain which progressed to severe pain. Additional reported symptoms included a 4-week history of fever, mental confusion that progressed to unconsciousness, and scleral icterus. He was evaluated Day 95 in the hospital with complaints of severe abdominal pain, facial puffiness, and right upper quadrant swelling. Findings included hepatosplenomegaly, edema, ascites, and an elevated creatinine. On Day 99, the subject died. No specific cause of death was provided.

Reviewer's comment: As the onset of liver disease would have preceded the development of cirrhosis by more than 3 months, the underlying liver disease would not be expected to be related to V920. The reported clinical findings suggest chronic hepatic disease, although limited clinical information was provided. It is unlikely that progression of hepatic disease 3 months after vaccination was related to V920.

For the above fatal reports, there is no obvious biologically plausible mechanism to suggest association with vaccination, some reports include confounding predisposing conditions, and most reports contain insufficient information for a full assessment of causality. There is no clear evidence to support a causal relationship of these events to V920, although a conclusive determination would require additional data.

A plausible alternative etiology was evident for the remaining fatal SAEs, including those with an onset prior to vaccination (nasopharyngeal carcinoma), those that were due to trauma or accident (electrocution, drowning, spinal cord injury, and skeletal injury), or those that were due to infection (HIV wasting syndrome, malaria [n= 2], and pyonephrosis).

6.4.12.4 Nonfatal Serious Adverse Events

In the 28 days after enrollment or vaccination, an SAE of malaria was reported by a safety sub-study subject in the Immediate Vaccination group and an SAE of Ludwig's

angina was reported by a safety sub-study subject in the Deferred Vaccination group. Neither event was considered related.

Through Month 1 in the full study population, 42 SAEs were reported by 20 subjects (0.6%) in the Immediate Vaccination group, 11 subjects (0.3%) in the Deferred-Crossover group, and seven subjects (0.3%) in the Deferred Vaccination group. As described above, three fatal SAEs were reported <30 days after vaccination; these are excluded from following table which summarizes the remaining 39 non-fatal SAEs by treatment group and vaccination status.

Table 53 Serious adverse events through Day 30 (Full safety population)

MedDRA Preferred Term	Immediate Vaccination (N= 3241) n (%)	Deferred Vaccination (N= 2615) n (%)	Deferred Vaccination Crossover (N= 3405) n (%)	All vaccinated (N= 6603) n (%)
Anxiety	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)
Appendicitis	1 (<0.1)	0 (0)	1 (<0.1)	2 (<0.1)
Diabetes mellitus	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)
Enteritis	0 (0)	0 (0)	1 (<0.1)	1 (<0.1)
Inguinal hernia*	3 (<0.1)	0 (0)	2 (<0.1)	5 (<0.1)
Fracture**	1 (<0.1)	1 (<0.1)	2 (<0.1)	3 (<0.1)
Hernia	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)
Hypovolemic shock	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)
Joint dislocation	0 (0)	2 (<0.1)	0 (0)	0 (0)
Laceration	0 (0)	1 (<0.1)	0 (0)	0 (0)
Ludwig angina	0 (0)	1 (<0.1)	0 (0)	0 (0)
Malaria	7 (0.2)	1 (<0.1)	1 (<0.1)	8 (0.1)
Peptic ulcer	3 (<0.1)	0 (0)	0 (0)	3 (<0.1)
Sickle cell anemia with crisis	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)
Toothache	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)
Typhoid fever	1 (<0.1)	1 (<0.1)	0 (0)	0 (0)
Umbilical hernia	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)
Ureterolithiasis	0 (0)	0 (0)	1 (<0.1)	0 (0)
Urinary tract infection	0 (0)	0 (0)	1 (<0.1)	1 (<0.1)

*Inguinal hernia used as a composite term (including events of inguinal hernia, inguinal hernia obstructive)
**Fracture used as a composite term (including events of forearm fracture, lower limb fracture, and clavicle fracture)
Source: Adapted from Original BLA 125690/1; V920-011 Clinical Study Report, p. 386-389, Table 14-36

Reviewer's comment: A direct comparison for the 30-day time period can only be made between the Immediate and Deferred Vaccination groups, as there was no comparator group for the post-vaccination period in the Deferred Vaccination Crossover group. Overall, more SAEs were reported in the Immediate Vaccination group compared to the Deferred Vaccination group, although none of the SAEs were considered related and the open-label study design confounds an interpretation of the differences between groups. In general, the sponsor's assessment of causality is appropriate and alternative etiologies for the reported events are identifiable. However, events of malaria and peptic ulcer disease were reported by a higher proportion of subjects in the Immediate Vaccination group compared to the Deferred Vaccination group. Some of the SAEs of malaria with a close temporal relationship to vaccine administration were diagnosed

clinically, and it is possible that the symptoms attributed to malaria (e.g., fever, chills, headache, and/or vomiting) were due to V920. Additionally, there were three reports of SAEs reported within the first several weeks following V920 that included symptoms of abdominal pain and other non-specific systemic complaints that were coded as peptic ulcer disease. These cases may indicate that reactogenicity associated with V920 can have severe manifestations, including abdominal pain, resulting in hospitalization for further assessment.

During the 6-month follow-up period, SAEs were reported by 54 subjects (1.3%) in the Immediate Vaccination group, 47 subjects (1.2%) in the Deferred-Crossover group, and 32 subjects (0.7%) in the Deferred Vaccination group, including the 24 subjects with fatal events. The Deferred Vaccination group had a shorter period for reporting of SAEs during the Randomized Portion (median follow-up time was 150 days compared to 180 days for the Immediate Vaccination group) as some subjects were vaccinated at the protocol specified 18-week time point. None of the SAEs were considered related to vaccine.

The following table summarizes all SAEs through 6 months reported by more than one subject in the Full safety population.

Table 54 Serious adverse events through Month 6 reported by more than one subject (Full safety population)

MedDRA Preferred Term	Immediate Vaccination (N= 4261) n (%)	Deferred Vaccination (N= 4308) n (%)	Deferred Vaccination Crossover (N= 3788) n (%)	All vaccinated (N= 7960) n (%)
Appendicitis	3 (<0.1)	0 (0)	1 (<0.1)	4 (<0.1)
Cellulitis	1 (<0.1)	1 (<0.1)	2 (<0.1)	3 (<0.1)
Cerebrovascular accident	0 (0)	0 (0)	2 (<0.1)	2 (<0.1)
Gastroenteritis	0 (0)	0 (0)	3 (<0.1)	3 (<0.1)
Inguinal hernia*	5 (0.1)	4 (<0.1)	5 (0.1)	10 (0.1)
Lower limb fracture	1 (<0.1)	0 (0)	1 (<0.1)	2 (<0.1)
Malaria	12 (0.3)	2 (<0.1)	3 (<0.1)	15
Pelvic inflammatory disease	1 (<0.1)	0 (0)	2 (<0.1)	3 (<0.1)
Peptic ulcer and peptic ulcer perforation	3 (<0.1)	1 (<0.1)	3 (<0.1)	6 (<0.1)
Urinary tract infection	1 (<0.1)	0 (0)	2 (<0.1)	3 (<0.1)
Uterine leiomyoma	2 (<0.1)	3 (<0.1)	0 (0)	2 (<0.1)

*Inguinal hernia used as a composite term (including events of inguinal hernia, inguinal hernia obstructive, and inguinal hernia strangulated)
Source: Adapted from Original BLA 125690/1; V920-011 Clinical Study Report, p. 342-349, Table 14-27

The SOCs with the greatest proportions of subjects reporting events were the Gastrointestinal disorders, Infections and infestations, Injury, poisoning and procedural complications SOCs with comparable proportions of subjects in each treatment group reporting.

Reviewer comment: SAEs were reported by a higher proportion of subjects in the Immediate Vaccination and Deferred-Crossover groups compared to the Deferred

Vaccination group; the difference was small (1.3% versus 0.7%) but statistically significant (p= 0.015). There was no statistically significant difference between the proportions of subjects in the Immediate and Deferred Vaccination groups reporting a specific PT. In an analysis of SAEs by person years, the difference between the groups persisted. The incidence of SAEs per 100 person years (95% CI) was 2.91 (2.22, 3.74), 1.99 (1.37, 2.79), and 2.73 (2.03, 3.60) in the Immediate, Deferred, and Deferred-Crossover groups, respectively. The relevance of this difference in the context of an open-label study in unknown.

The study sponsor did not attribute any of the SAEs to vaccination and review of the nature of these SAEs (describing events such as medical or surgical issues [e.g., hypertensive emergency, nephrolithiasis, appendicitis], cancer, trauma, endemic infections such as malaria or gastroenteritis) did not reveal a pattern consistent with a causal relationship to vaccination.

6.4.12.5 Adverse Events of Special Interest (AESI)

A total of 261 gestational events were reported during the study. After an amendment on February 10, 2106, only pregnancies with onset (pregnancy onset defined by the estimated date of last menstrual period [LMP]) within 2 months after enrollment or vaccination. A total of 107 pregnancies were reported as occurring within two months after enrollment or vaccination. One subject was 5 months pregnant at the time of vaccination, which was apparently unrecognized; the outcome of this pregnancy was a live preterm delivery (<37 weeks gestation).

Reviewer's comment: According to the CSR, only pregnancies with LMP 60 days after enrollment or vaccination were followed. However, the study datasets include 107 pregnancies that include LMP within 60 days before or after enrollment or vaccination. This is appropriate as it allows for the assessment of pregnancies that were very early or unrecognized at the time of vaccination. The subject who was 5 months pregnant at the time of vaccination was identified in the datasets. This was not included as a protocol deviation and is not discussed in the CSR. As above, this was addressed by the Applicant in response to an IR; no additional information is available.

In the CSR, the pregnancy data were tabulated by treatment assignment group and not by vaccination status. To assess the impact of vaccination on pregnancy outcome, multiple IRs were sent to the Applicant to clarify pregnancy outcomes by vaccination status at the time of onset of pregnancy. The Applicant provided recalculated pregnancy outcome data; however, there remained some discrepancies between the Applicant's tabulation of pregnancy outcome data and SDTM datasets provided to the BLA. The following table was generated from the SDTM datasets and differs slightly from the tabulation provided by the Applicant. However, the minor discrepancies are not considered clinically relevant.

The following table describes pregnancies reported during the study.

Table 55 Outcomes of pregnancies ongoing at the time of vaccination or with onset within 60 days of enrollment or vaccination by vaccination status at the time of pregnancy

	Vaccinated N= 61	Unvaccinated N= 46

	n (%)	n (%)
Pregnancy loss <20 weeks	21 (34.4)	9 (19.6)*
Pregnancy loss >20 weeks	3 (4.9)	6 (13.0)
Live birth (term and preterm)	34 (55.7)	24 (52.2)
Unknown or not followed to outcome	3 (4.9)	7 (15.2)

*including 2 elective abortions, the proportion of subjects with spontaneous abortions only is 15.2%%
Source: Original BLA 125690/1 pnf.xpt; vac.xpt; 125690/51 and 125690/55 (Responses to IRs)

Subjects with LMP <60 days prior to vaccination would be those subjects most likely to have implanted embryos during the time of vaccine viremia. Of the 16 vaccinated subjects with LMP <60 days prior to vaccination, nine (56.3%) resulted in a live birth, six (37.5%) resulted in early pregnancy loss, and one (6.2%) outcome was unknown. Of the 44 vaccinated subjects with LMP 0 to 60 days after vaccination, 24 (54.5%) resulted in a live birth, 15 resulted in early pregnancy loss (34.1%), three resulted in stillbirth (6.8%), and two (4.5%) were not followed to outcome. The remaining vaccinated subject was 5 months pregnant at the time of vaccination as described above and delivered a live, pre-term infant.

Reviewer's comment: An imbalance in the proportions of pregnancies resulting in early pregnancy loss is noted, with 34.4% of pregnancies resulting in spontaneous early loss after vaccination compared to 15.2% of unvaccinated subjects. Conversely, the proportions of pregnancies resulting in stillbirth (≥20 weeks of gestation) was higher in unvaccinated subjects (13.0%) compared to vaccinated subjects (4.9%). The imbalance in early losses seen for vaccinated subjects is of concern. However, several factors limit a conclusive interpretation of the data:

- *There is missing information on 15.2% of pregnancies in unvaccinated subjects and 4.9% of vaccinated subjects.*
- *LMP dates are based on subject recall and gestational dating of early pregnancies by ultrasound was not provided; therefore, the reliability of the LMP is questionable and estimates of the onset of pregnancy may be subject to bias.*
- *The open-label design of the study may have impacted the reporting of early pregnancy losses which were not managed medically. Unvaccinated subjects may have been less motivated to report pregnancy outcomes.*

To address this potential safety concern, the Applicant will collect and provide post-marketing data on pregnancy outcomes for all vaccinees, including data from the ongoing and completed expanded access programs in the DRC, in which pregnancy is not an exclusion criterion for vaccination.

In a recent review of pregnancy outcomes in the setting of maternal EVD, data for 59 confirmed or suspected Zaire ebolavirus cases in pregnancy was reviewed; of these 59 cases, 47 resulted stillbirths or miscarriages (78%) and 12 resulted in live births (22%), all of whom died within 19 days of life (Bebell, 2017). In light of the risks of EVD to the mother and fetus and the potential for adverse effects of vaccination on the fetus as well as the benefits of vaccination, the decision to vaccinate pregnant women or women planning to become imminently pregnant should consider the risk of exposure to Ebola virus and whether exposure is avoidable (i.e. for those traveling or deploying to an outbreak setting).

6.4.12.6 Clinical Test Results

Laboratory tests (hematology, blood chemistry, urinalysis) were not routinely conducted as part of the protocol for this study.

6.4.12.7 Dropouts and/or Discontinuations

No subjects discontinued from the study due to adverse events following vaccination.

6.4.13 Study Summary and Conclusions

V920-011 was an open-label, randomized study designed to evaluate the efficacy and safety of a single dose of V920 in a population of at-risk HCWs and Ebola front-line workers in Sierra Leone. Eligible subjects were enrolled and individually randomized 1:1 to receive a single IM dose of V920 at 2×10^7 pfu in the Immediate Vaccination group or the Deferred Vaccination group. Immediate vaccination was defined as vaccination within 7 days of enrollment, and deferred vaccination was defined as vaccination at the end of an 18 to 24-week follow-up period (at which point vaccinated members of this group are referred to as the Crossover Vaccination group).

Humoral immunogenicity as measured by GP-ELISA and PRNT was demonstrated by the immunogenicity subset (n= 508) at each post-vaccination time point, with a peak in GP-ELISA GMT at Month 1 and comparable elevated PRNT GMTs at each time point. Humoral immune responses were detectable at Month 9 to 12.

Injection site events were commonly seen after V920, with 80% of subjects in the Immediate Vaccination safety sub-study reporting mild to moderate injection site events. Solicited systemic events were reported more commonly after V920 than post-enrollment in the Delayed Vaccination group, including severe events of pyrexia. Headache, fever, and fatigue were the most commonly reported events between Days 1 to 28. Each of the solicited systemic adverse events were reported by a higher proportion of subjects post-vaccination in the Immediate Vaccination group compared to the Deferred Vaccination group. Arthralgia events were reported by 39% of vaccinated subjects, most of which occurred in the week following vaccination. Joint swelling was reported by 3.4% of vaccinated subjects. Events of rash and vesicular rash were reported by a higher proportion of vaccinated subjects (12% and 4.4%, respectively) than unvaccinated subjects (2.2% and 0.9%, respectively). The proportion of subjects with SAEs was higher in the Immediate Vaccination group; none of the SAEs were considered related to V920 by the study Sponsor and no pattern of SAEs suggestive of a safety signal was identified. However, multiple fatal SAEs did not have sufficient diagnostic information to allow for a full interpretation of the events. Additionally, some SAEs were attributed to alternative etiologies (*e.g.*, malaria, peptic ulcer disease) without diagnostic confirmation which were temporally related to vaccination and manifested with symptoms potentially attributable to vaccine reactogenicity, suggesting that reactogenicity may be severe/serious in some cases.

7. Integrated Overview of Efficacy

V920-010 is the sole efficacy study submitted to the BLA. Therefore, no integration of efficacy data was conducted. Please see Section 6.1 for the full clinical review of V920-010, including efficacy data and analyses.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

A summary of the types of adverse events and collection time points in the V920 clinical program is provided in the following table:

Table 56 Types of adverse events and collection time points for V920 studies

Trial Number	Trial Design and Blinding Status	Subject Memory Aid Use (Yes or No)	CSR MedDRA Version	AE Category				
				Solicited Injection-Site and Systemic Adverse Events	Unsolicited Adverse Events	Serious Adverse Events	Viremia and Viral Shedding	Clinical Laboratory Safety Tests
V920-001	Randomized, double-blind	Yes	17.0	Day 1 to 14	Day 1 to 28	Day 1 to 180	Day 0,1, 3, 7, 14	Day 0, 1, 3, 7, 28, 180
V920-002†	Randomized, double-blind	Yes	17.0	Day 1 to 14	Day 1 to 28	Day 1 to 365	Day 0, 3, 7 following each dose	Day 0, 7, 28, 35, 56 following each dose
V920-003	Randomized, double-blind	Yes	17.0	Day 1 to 14	Day 1 to 28	Day 1 to 180	Day 0, 1, 3, 7, 14	Day 0, 1, 3, 7, 28, 180
V920-004	Randomized, double-blind	Yes	17.0	Cohort 1: Day 1 to 14 Cohort 2: Day 1 to 56	Cohort 1: Day 1 to 28 Cohort 2: Day 1 to 56	Day 1 to 360	Day 0, 1, 2, 3, 4, 7, 14, 28	Day 0, 7, 28
V920-005	Randomized, double-blind	Yes	17.0	Day 1 to 14	Day 1 to 28	Day 1 to 365	Day 0, 1, 3, 7	Day 0, 1, 3, 7, 14, 28, 365(only blood count at Day 365)
V920-006	Open-label	Yes	17.0	Day 1 to 14	Day 1 to 28	Day 1 to 180	Day 0, 1 to 7, 14, 28	Day 0, 1, 3, 7, 14, 28, 180
V920-007	Open-label	Yes	17.0	Day 1 to 14	Day 1 to 28	Day 1 to 365	Day 0, 1, 2 and 7	Day 0, 1, 2, 7, 28, 84, 180, 365
V920-008	Open-label	Yes	17.0	Day 1 to 14	Day 1 to 28	Day 1 to 365	Day 0, 1, 3, 7	Day 0, 7, 30
V920-009‡	Randomized, double-blind	No	20.0	Week 1, Week 2, Month 1	Week 1 and Month 1	Week 1, Month 1 and 2, every 2 months to trial end	Not collected	At Week 1 and Month 1
V920-010§	Randomized ring vaccination, open-label	No	Not applicable	Minute 30, Day 3 and Day 14	Day 1 to 14	Day 1 to 84	Not collected	Not collected
V920-011	Randomized, open-label	Yes	19.0	Safety Sub-Study subjects: Day 0 to 28	Overall Population: Day 0 to 28	Overall Population: Day 0 to 180	Not collected	Not collected
V920-012	Randomized, double-blind	Yes	19.1	Day 1 to 42*	Day 1 to 42	Day 1 to Month 24	Not collected	As needed for arthralgia, arthritis, rash or vesicles follow-up only

† Subjects in the V920-002 trial received 2 doses of V920 on Days 0 and 28 postvaccination. Data for subjects who received the second dose are presented separately from subjects who received a single dose in this Summary of Clinical Safety.
‡ The V920-009 trial did not collect a specific AE onset date or stop date; all other trials collected AE onset and stop dates for solicited AEs.
§ Adverse events were not encoded using MedDRA for the V920-010 trial.
* Injection-site AEs were solicited from Day 1 to 5 postvaccination in the V920-012 trial; joint and skin events were solicited from Day 1 to 42. No other solicited systemic AEs were collected in this trial.

[Ref. 5.3.5.1: P001, P002, P003, P004, P005, P006, P007, P008, P009V920, P010V920, P011, P012V01V920] [Ref. 5.3.5.3: 04MCC8]

Source: Original BLA125690/1, Summary of Clinical Safety p. 25-26, Table 2.7.4:2

Reviewer's comment: As the ISS analysis is limited to SAEs reported in the blinded studies and includes a limited proportion of the total number of subjects exposed to V920 in the clinical development program, this section of the review includes both the ISS and summaries of safety data from all Phase 2/3 studies. Despite variations in the methods for safety data collection, the sum total of safety data from all 15,997 adult subjects exposed to V920 allows for an adequate assessment of reactogenicity, unsolicited events, and SAEs.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

In the Summary for Clinical Safety (SCS), safety data from all 12 studies submitted to the BLA were provided.

In the Integrated Summary of Safety (ISS), only data from double-blinded studies were provided, including studies V920-001, V920-002, V920-003, V920-004, V920-005, V920-009, and V920-012. AEs were coded using MedDRA version 20.0.

The study populations used for the safety analysis in each study are as follows:

- V920-010: All Subjects Vaccinated population, consisting of all subjects from the immediate, delayed, or non-randomized vaccination groups who received one dose of study vaccine.
- V920-011: Safety sub-study population and overall study population, including all subjects with at least one documented safety assessment in the follow-up time period.
- All remaining studies: All Subjects as Treated (ASaT) population, consisting of all randomized subjects who received one dose of study vaccine and had any safety follow-up.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Exposure

Overall

In total, 16,765 male and female adult subjects (≥18 years of age) participated in the 12 studies conducted in the clinical development program. A total of 15,997 subjects received V920 and 15,399 subjects received the 2×10^7 pfu or higher dose of V920. The majority of subjects were exposed to V920 in studies V920-010 (n= 5642) and V920-011 (n= 13,825).

Pooled data

In the blinded studies included in the ISS, 2,171 subjects received V920 and 1,712 subjects received the 2×10^7 pfu or higher dose of V920. The following table summarizes the number of subjects from each study included in the ISS:

Table 57 Summary of exposure to V920 by study for subjects included in the integrated summary of safety

Study	V920 <2 x 10^7 pfu	V920 ≥2 x 10^7 pfu	V920 total	Placebo
V920-001	10	20	30	9
V920-002	10	20	30	9
V920-003	30	0	30	10
V920-004	323	95	418	94
V920-005	86	16	102	13
V920-009	0	500	500	498
V920-012	0	1061	1061	133

Source: Original BLA 125690/1; Integrated summary of safety, p. 10, adapted from table 5.3.5.3.3

Reviewer's comment: Of the 1061 subjects in V920-012 who received ≥2 x 10^7 pfu V920 and were included in the ISS dataset, ten did not have safety follow-up and were excluded from the ASaT population (See Section 6.3.10 [Study Population and Disposition]). However, these subjects were included in the overall ISS dataset.

Demographics

Table 58 Demographics of subjects included in integrated summary of safety

	V920 <2 x 10^7 pfu N=459 n (%)	**V920 ≥2 x 10^7 pfu N=1712 n (%)**	**V920 total N=2171 n (%)**	**Placebo N=766 n (%)**
18- 65 YOA	459 (100)	1707 (99.7)	2166 (99.8)	755 (98.6)
>65 YOA	0 (0)	5 (0.3)	5 (0.2)	11 (1.4)
Female	228 (49.7)	800 (46.7)	1028 (47.4)	314 (41.0)
Male	231 (50.3)	912 (53.3)	1143 (52.6)	452 (59.0)
American Indian or Alaska Native	2 (0.4)	7 (0.4)	9 (0.4)	1 (0.1)
Asian	6 (1.3)	11 (0.6)	17 (0.8)	5 (0.7)
Black or African American	120 (26.1)	852 (49.8)	972 (44.8)	577 (75.3)
Multiple	1 (0.2)	16 (0.9)	17 (0.8)	1 (0.1)
Native Hawaiian or other Pacific Islander	1 (0.2)	3 (0.2)	4 (0.2)	1 (0.1)
Other	5 (1.1)	1 (0.1)	6 (0.3)	0 (0)
White	322 (70.1)	822 (48.0)	1144 (52.7)	181 (23.6)
Unknown	2 (0.4)	0 (0)	2 (0.1)	0 (0)

YOA= years of age
Source: Original BLA 125690/1; adapted from ADSL dataset for ISS

Reviewer's comment: The ISS pooled safety population was well matched across treatment and placebo groups for age and sex. However, the proportions of Black or African-American subjects were higher in the placebo group compared to the V920 treatment groups because V920-009 (conducted in Liberia) contributed the largest number of subjects to the placebo group compared to all other studies.

8.2.3 Categorization of Adverse Events

The SAE data in the ISS were encoded by MedDRA version 20.0.

Reviewer's comment: Adverse event coding quality was assessed as part of the data validation report and was conducted using the FDA Validator tool. Adverse event coding was reviewed for the Phase 2/3 studies. For the blinded studies, V920-009 and V920-012, no concerns with MedDRA coding were identified. In V920-010, a total of 100 subjects reported multiple adverse events in the ADAE datasets that were not individually coded from verbatim term to a MedDRA PT, but instead were coded as a group to a MedDRA PT of "Ill-defined disorder" for each subject. In response to an Information Request for the rationale for this coding strategy, the Applicant indicated that the study Sponsor collected adverse event data using open text fields; thus, multiple events were coded to a single PT of "Ill-defined disorder" to maintain data traceability. Therefore, data for these subjects are not coded in a manner that allows for complete safety data tabulation.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

As discussed in Section 8.1, the studies of V920 were conducted by multiple sponsors using different study designs in different geographical regions. Many factors precluded a more extensive pooling of safety data, including differences in methods for data collection, type of contacts with subjects (e.g., phone contact versus in-person visits), duration and methods of collection of solicited and unsolicited adverse events, specific solicited events (including solicitation of joint and skin-related adverse events), grading criteria for adverse events and laboratory findings, timing of clinical laboratory assessments, and the determination of investigator-assessed relatedness (in some studies, relatedness was assessed only for Grade 3 or above AEs or SAEs).

Due to these differences, the pooled analysis in the Integrated Summary of Safety (ISS) was limited to SAEs reported in blinded clinical studies, including Phase 1 studies. Events were analyzed by dose level relative to the dose selected for clinical use. In the Summary of Clinical Safety, safety findings were analyzed by study and descriptions were grouped together based on the study design (i.e. open-label or blinded).

The duration of collection of SAEs in the studies included in the ISS was 12 months for V920-002, V920-004, V920-005, and V920-009 and 6 months for V920-001, V920-003, and V920-012. At the time of integration, safety data from Months 6 to 24 of study V920-012 were not available. These data are reported separately and are included in the individual study review for V920-012 (Section 6.3).

Reviewer comments: Due to more uniform collection methods for SAEs across blinded trials, this subset was chosen for use in an integrated safety analysis; however, differences in the design and conduct of each study as described above limits interpretation of the pooled data.

8.4 Safety Results

8.4.1 Deaths

ISS pooled dataset

Fatal SAEs were reported in six of 766 placebo recipients (0.8%) in the ISS dataset compared to eight of 2,171 V920 recipients (0.4% for all V920 doses). Of subjects who received ≥2 x 10^7 pfu of V920 (n= 1,712), seven (0.4%) experienced fatal SAEs. The following table describes fatal SAEs in the ISS dataset by time of onset, all of which were considered not related to study product by the Investigator.

Reviewer's comment: Excluding the ten subjects who were not included in the ASaT population from V920-012 from the total number of V920 recipients does not change the overall proportion of subjects with fatal SAEs (i.e., 0.4% of V920 recipients).

Table 59 Fatal SAEs reported in the ISS dataset

Study	Dosing group	Age (years)/Sex	Serious adverse event(s)	Study day of onset
V920-009	Placebo	18/Female	*Pneumocystis jirovecii* pneumonia	22
V920-009	Placebo	30/Male	Renal failure/malignant hypertension/renal failure (fatal)	34/43/60
V920-009	Placebo	27/Female	Pulmonary tuberculosis	113
V920-009	Placebo	28/Male	Pulmonary tuberculosis	244
V920-009	Placebo	47/Female	Sudden death	316
V920-009	Placebo	52/Female	Multiple organ dysfunction syndrome	331
V920-009	2 x 10^7 pfu	35/Female	Respiratory failure	41
V920-012	2 x 10^7 pfu	47/Male	Hepatic failure	76
V920-009	2 x 10^7 pfu	56/Male	Death	78
V920-004	3 x 10^6 pfu	22/Male	Head injury	120
V920-012	2 x 10^7 pfu	64/Female	Craniocerebral injury	152
V920-009	2 x 10^7 pfu	74/Male	Malignant hypertension	218
V920-009	2 x 10^7 pfu	24/Male	Pulmonary tuberculosis	223
V920-009	2 x 10^7 pfu	42/Male	Death	273

Source: Original BLA 125690/1, adapted from ADSAE dataset for ISS

Reviewer's comment: Detailed summaries of the fatal adverse events in V920-009 and V920-012 are provided in the respective individual reviews of each study (Sections 6.2 and 6.3, respectively). The fatal events in V920-012 had clear alternative etiologies and were not temporally related to V920 administration; the assessment that the events were not related to V920 is appropriate. The fatal events in V920-009 after V920 include three events of death for which there was no diagnostic information or autopsy results, precluding a full assessment of causality; however, these fatal events were temporally remote from vaccination and a sudden death was also reported after placebo. For the remaining fatal events in V920-009, a plausible alternative etiology was provided (infectious, complications of AIDS, and malignant hypertension leading to death); the assessment that the events were not related to V920 is appropriate. The fatal event of head injury in V920-004 was the result of a motorcycle accident and was not related to V920.

In addition to fatal events reported in the ISS dataset, one additional fatality due to a road traffic accident was reported in the V920-012 extension study (including events reported between Months 6 and 24 post-vaccination).

Open-label studies

Fatal SAEs were reported by 18 vaccinated subjects in V920-010 during the 84 day follow up period. An additional subject died on Day 86. All deaths were considered unrelated to study product. In V920-011, 25 subjects (0.2%) experienced SAEs that resulted in death. During the 6-month follow-up period, eight subjects (0.2%) in the Immediate Vaccination group, 11 subjects (0.3%) in the Deferred-Crossover group (SAE reported in Deferred Vaccination group, death occurred during Deferred-Crossover period), and six subjects (0.1%) in the Deferred Vaccination group died, including one subject who died during post-6 month follow-up. None of the deaths were attributed to vaccination. The following table summarizes the deaths in open-label studies by MedDRA PT, excluding deaths due to EVD (including a death due to malaria and EVD) as these were considered an efficacy endpoint.

Table 60 Fatal adverse events in open-label studies, excluding Ebola virus Disease

Study	Dosing group	Age (years)/Sex	MedDRA Preferred Term	Study day of onset
V920-010	2 x 10^7 pfu	53/Male	Sudden cardiac death	11
V920-010	2 x 10^7 pfu	70/Male	Sudden death	81
V920-010	2 x 10^7 pfu	81/Male	Sudden death	86
V920-010	2 x 10^7 pfu	41/Female	HIV infection CDC Group IV subgroup C2 (also infection with tuberculosis, not MedDRA coded)	35
V920-010	2 x 10^7 pfu	60/Male	Appendicitis	61
V920-010	2 x 10^7 pfu	56/Female	Tumor ulceration	65
V920-011	2 x 10^7 pfu	40/Female	Nasopharyngeal cancer	-80**
V920-011	2 x 10^7 pfu	22/Male	Death	11
V920-011	2 x 10^7 pfu	31Male	Skeletal injury	21
V920-011	2 x 10^7 pfu	52/Female	Cerebrovascular accident	60
V920-011	2 x 10^7 pfu	24/Male	Loss of consciousness	63
V920-011	2 x 10^7 pfu	37/Female	Malaria	64
V920-011	2 x 10^7 pfu	32/Female	HIV wasting syndrome	66

Study	Dosing group	Age (years)/Sex	MedDRA Preferred Term	Study day of onset
V920-011	2 x 10^7 pfu	57/Male	Hemorrhagic stroke	74
V920-011	2 x 10^7 pfu	23/Male	Electrocution	83
V920-011	2 x 10^7 pfu	52/Male	Acute abdomen	84
V920-011	2 x 10^7 pfu	27/Male	Pancreatitis	88
V920-011	2 x 10^7 pfu	33/Male	Hepatic cirrhosis	90
V920-011	2 x 10^7 pfu	30/Male	Malaria	118
V920-011	2 x 10^7 pfu	43/Male	Pyonephrosis	134
V920-011	2 x 10^7 pfu	50/Female	Myocardial infarction	136
V920-011	2 x 10^7 pfu	53/Female	Subarachnoid hemorrhage	146
V920-011	2 x 10^7 pfu	21/Male	Drowning	166
V920-011	2 x 10^7 pfu	56/Male	Spinal column injury	172
V920-011	2 x 10^7 pfu	29/Male	Encephalitis	179
V920-011	Deferred*	54/Male	Peptic ulcer perforation	6
V920-011	Deferred*	37/Male	Renal failure	49
V920-011	Deferred*	29/Male	Hepatocellular carcinoma	113
V920-011	Deferred*	22/Female	Sickle cell anemia with crisis	117
V920-011	Deferred*	54/Male	Pulmonary tuberculosis	179
V920-011	Deferred*	35/Female	Postpartum hemorrhage	272

*Subjects in the deferred group were not vaccinated at the time of the onset of the fatal event
**The diagnosis for this subject occurred prior to vaccination in the Deferred Vaccination time period; the subject died from the diagnosis after vaccination in the Deferred-Crossover time period.
Source: Original BLA 125690/1, adapted from ADSAE dataset for ISS

Reviewer comments: Detailed summaries of the fatal adverse events in V920-010 and V920-011 are provided in the respective individual reviews of each study (Sections 6.1 and 6.4, respectively). There were limited data available for the majority of fatal events in V920-011, which precluded a full assessment of causality.

In V920-011, fatal cerebrovascular events were reported for three subjects after V920 and an additional non-fatal serious event of cerebrovascular accident was reported 77 days after V920. Neurovascular events were only reported after V920, although it was difficult to compare frequencies due to the open-label design of the study and the shorter follow up time for subjects in the Deferred Vaccination group. Please see Section 8.4.8 for an additional review of neurovascular events in the V920 clinical development program.

In V920-011, seven fatal events were reported after V920 where no clear etiology for death was identified, including two reports characterized by the sudden onset of loss of consciousness and hallucinations in young healthy males who died shortly after the onset of symptoms. Both events were temporally distant from vaccination (62 and 178 days, respectively), at a time when vaccine viremia would no longer be expected, and could have toxicologic or infectious etiologies, although there is no or limited diagnostic data provided in case narratives. Similar cases were not observed in other studies. A third report describes a young man with tachypnea, loss of appetite, fatigue, weakness, joint pain, muscle pain and headache 10 days after vaccination who left the hospital against medical advice and died 8 days later of an unknown cause. Reports of fatal events of acute abdomen, myocardial infarction, liver cirrhosis, and pancreatitis did not include sufficient information to assess the cause of death. A definitive assessment of causality for these cases was precluded by the limited data available.

8.4.2 Serious Adverse Events

ISS pooled dataset
The Applicant's SAE analysis was performed on all SAEs, including fatal SAEs. The numbers and proportions of subjects reporting at least one SAE by time period and dose group is described in the following table:

Table 61 Subjects reporting at least one SAE by time period and dose group

Subjects with serious adverse events	**V920 <2 x 10^7 pfu N=459 n (%)**	**V920 ≥2 x 10^7 pfu N=1712 n (%)**	**V920 total N=2171 n (%)**	**Placebo N=766 n (%)**
Day 1 to 28 post-vaccination	0 (0)	9 (0.5)	9 (0.4)	11 (1.4)
Day 1 to 180 post-vaccination	3 (0.7)	54 (3.2)	57 (2.6)	48 (6.3)
Day 1 to 365 post-vaccination	6 (1.3)	68 (4.0)	74 (3.4)	60 (7.8)

Source: Adapted from Original BLA 125690/1, ISS, p. 13, 15, 19; Tables 5.3.5.3.3:5, 5.3.5.3.3:6, 5.3.5.3.3:7

In the Day 1 to 28 post-vaccination time period, a higher proportion of subjects in the placebo group reported one or more SAEs (n= 11; 1.3%) compared to the combined V920 groups (n= 9; 0.4%). Of V920 recipients, SAEs were only reported by subjects in the ≥2 x 10^7 pfu group (n= 9; 0.5%). Malaria was the only MedDRA PT reported by more than one subject in any group (reported by 0.4% of subjects in the ≥2 x 10^7 pfu group and 0.9% of subjects in the placebo group). The greatest proportions of subjects reported events in the Infections and infestations MedDRA System Organ Class (SOC). Other SAEs reported after V920 included hyperthyroidism, hyperglycemic hyperosmolar nonketotic syndrome, and asthma.

Reviewer's comment: In the time period immediately following vaccination, SAEs were uncommon. Narrative details for the three SAEs that were not malaria were provided in the individual clinical reviews. None were considered related by the Investigator, and each of the events was reported by a subject with a prior history of the event. The assessment that the events were not related to V920 is appropriate.

Excluding the ten subjects who were not included in the ASaT population from V920-012 from the total number of V920 recipients does not change the overall proportion of subjects with SAEs for each time period.

In the Day 1 to 180 post-vaccination time period, a higher proportion of subjects in the placebo group reported one or more SAEs (n= 48; 6.3%) compared to the combined V920 groups (n= 57; 2.6%). MedDRA PTs reported by more than one subject included malaria (reported by 1.2% of subjects in the ≥2 x 10^7 pfu group and 4.8% of subjects in the placebo group), gastroenteritis, basal cell carcinoma, and pulmonary embolism (each reported by 0.1% of subjects in the ≥2 x 10^7 pfu group [n= 2] and 0% of subjects in the placebo group). The greatest proportions of subjects reported events in the Infections and infestations MedDRA System Organ Class (SOC).

In the Day 1 to 365 post-vaccination time period (limited to Day 1 to Day 180 in protocols 001, 003, and 012), a higher proportion of subjects in the placebo group reported one or more SAEs (n= 60; 7.8%) compared to the combined V920 groups (n= 74; 3.4%).

Reviewer's comment: Interpretation of the proportions of subjects reporting SAEs during the Day 1 to 365 time period is confounded by the inclusion of subjects in V920-012, V920-001, and V920-003 in the denominators for the subject population, although these subjects did not provide safety follow up from Day 180 to 365.

MedDRA PTs reported by more than one subject after V920 included malaria (reported by 1.9% of subjects in the ≥2 x 10^7 pfu group and 5.6% of subjects in the placebo group), gastroenteritis (reported by 0.2% of subjects in the ≥2 x 10^7 pfu group and 0% of subjects in the placebo group), death, fetal death, basal cell carcinoma, cerebrovascular accident, and pulmonary embolism (each reported by 0.1% of subjects in the ≥2 x 10^7 pfu group [n= 2] and 0% of subjects in the placebo group). An event of hepatic failure was reported by a subject in V920-012 with a history of alcoholism and alcoholic pancreatitis. The greatest proportions of subjects reported events in the Infections and infestations MedDRA System Organ Class (SOC).

Reviewer's comment: In the 6-month and 1-year time period following vaccination, malaria remained the most commonly reported SAE. The observed SAEs were generally consistent with expected events in the study populations. A review of the deaths of unknown cause are discussed above in Section 8.4.1. A review of fetal deaths from V920-009 is in the individual study review (Section 6.2) and Section 9.1.1. Please see Section 8.4.8 for a review of neurovascular and thrombotic events.

Related SAEs
A total of four SAEs in the ISS dataset (all from study V920-009) were considered related to the study product by the Investigator, including events of vaginal hemorrhage and malaria in the placebo group and two events of malaria in the V920 group. These events were not considered related by the study Sponsor's medical officer for V920-009.

Reviewer's comment: As malaria is endemic in Liberia and events of malaria were consistently reported by a higher proportion of subjects after placebo compared to V920, it is unlikely that these specific malaria events are related to V920.

Open label studies
In the open-label Phase 1 studies, SAEs were reported in studies V920-007, V920-010, and V920-011.

In V920-007, SAEs were reported by 10 subjects, four of whom reported malaria. The remaining SAEs included appendicitis (n= 2), snake bite, gastritis, glaucoma, and excess bleeding post-tooth extraction.

In V920-010, SAEs were reported by 61 of the 5,643 vaccinated adult subjects during the 84 day follow up period. Excluding events of EVD and malaria, SAEs reported by more than one subject after V920 included anaphylaxis (n= 2), appendicitis (n= 3, including a fatal event), sudden death (n= 2), infection (n=2), and pyrexia (n= 2).

In V920-011, SAEs were reported by the following proportions of subjects in each study group during the 6-month follow up period: Immediate (54 of 4,261;1.3%), Deferred (32 of 4,308; 0.7%), and Deferred-Crossover (47 of 3,788; 1.2%). SAEs reported by a higher proportion of subjects after V920 than placebo and by more than one subject included

sickle cell anemia with crisis (n= 2) and cerebrovascular accident/hemorrhagic stroke (n= 3).

Under the Nervous system disorders SOC, a total of 6 V920 recipients reported SAEs compared to one subject in the Deferred group (unvaccinated), including events of aphasia, cerebrovascular accident (n= 2), hemorrhagic stroke, loss of consciousness, and subarachnoid hemorrhage. The unvaccinated subject in the Deferred Group reported an event of loss of consciousness. The event of aphasia was not associated with neurologic findings and spontaneously resolved. The event of loss of consciousness was attributed to physical violence.

Reviewer's comment: The available details for the SAEs reported in the open label studies are reviewed in the individual study sections (Section 6). Conclusions about relatedness to V920 were precluded by the lack of blinded comparator groups, varying duration of follow up for SAEs between studies and within study groups (V920-011), and the limited information provided in some narratives. Please see Section 8.4.8 for a review of neurovascular and thrombotic events. No other patterns consistent with a safety signal were identified.

Related SAEs
Related SAEs were only reported in V920-010, including events of febrile reaction, anaphylaxis (n= 2), pyrexia, infection, and influenza-like illness.

Reviewer's comment: The Sponsor's assessment of causality for these events is appropriate. Two events of anaphylaxis were reported with temporal association to vaccine and were considered related. Please see Section 6.1.12 for details of these events.

8.4.3 Study Dropouts/Discontinuations

No subjects discontinued from the clinical studies due to an AE, other than fatal events.

8.4.4 Common Adverse Events

See Sections 8.4.6 and 8.4.7 for a discussion of common local and systemic adverse events.

8.4.5 Clinical Test Results

Clinical laboratory safety data was collected systematically in the Phase 1 blinded clinical studies and in V920-009. In the Phase 1 studies, reference ranges were supplied by the study-specific laboratory. In the Phase 1 studies, grading scales for hematology laboratories were study-specific and were not consistent across all studies. In V920-009, laboratory test results were graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004.

<u>Hematology</u>

Across the Phase 1 blinded studies, decreases in leukocyte count, lymphocyte count, and neutrophil count were observed in a higher proportion of subjects after V920 compared to placebo. These decreases were generally reported by the highest

proportions of subjects at Days 1 and 3 (obtained in V920-001, V920-003, and V920-005 only). By Day 7, the proportions of subjects reporting decreases in these hematologic parameters were lower and most had resolved by Day 28. Most decreases in hematologic parameters were Grade 1 to 2 in severity. The following Grade 3 hematologic abnormalities were reported: a Grade 3 decrease in lymphocytes on Day 28 (V920-004), a Grade 3 decrease in neutrophils on Day 3 (V920-003), 9 subjects (30% of V920 recipients) with Grade 3 decreases in lymphocyte count on Day 1 (V920-001), and 10 subjects (9.8% of V920 recipients) with Grade 3 decreases in lymphocyte count on Day 1 (V920-005).

In V920-009, the proportions of subjects with abnormalities in hematology laboratories were generally comparable at the Week 1 visit. However, an imbalance was seen in the proportions of subjects with abnormalities in neutrophil counts. In the V920 group, 20.9% of subjects had Grade 1 (15.2% of subjects), 2 (4.6% of subjects), or 3 (1% of subjects) decreases in neutrophil count at the Week 1 visit compared to 9.7% of subjects in the placebo group with Grade 1 (7.3% of subjects), 2 (1.6% of subjects), or 3 (0.8% of subjects) decreases in neutrophil count. By the Month 1 visit, the proportion of subjects with abnormalities in neutrophil count was comparable between the groups and no other imbalances in hematologic abnormalities was noted.

Chemistry
Across the Phase 1 blinded studies and in V920-009 increases in ALT and AST were generally reported by a comparable proportion of subjects after V920 and placebo.

8.4.6 Systemic Adverse Events

Considerations in the interpretation of systemic adverse event data include:

- Data presented for V920-003 are limited to data collected after the first dose of vaccine.
- In V920-012, solicited systemic events were limited to: arthralgia, arthritis, rash, vesicular lesions, and temperature elevations (based on the daily recordings of temperatures by each subject) and were collected from Days 1 to 42 post-
- In V920-009 and V920-010, only SAEs were assessed for relatedness to V920, and in the V920-011 trial, only Grade 3 AEs for the safety sub-study and all SAEs were assessed for relatedness. In the V920-012 trial, all AEs were assessed for causal relationship to the study vaccine.

<u>Solicited systemic events</u>
Blinded studies
In the Phase 1 blinded studies, a higher proportion of subjects in the V920 groups reported solicited systemic events (59.6 to 98.3%) compared to subjects in the placebo group (33.3 to 100%) through Day 14. In each of the dose groups where the dose was 2 x 10^7 pfu or higher, solicited systemic events were reported by 64.6% to 100% of subjects. The proportions of subjects reporting each solicited systemic event varied between the Phase 1 blinded studies but were generally higher for each event after V920 compared to placebo. The following solicited systemic events were the most commonly reported by subjects who received ≥2 x 10^7 pfu V920: chills (27.7% to 70%), fatigue (38.3% to 90%), headache (43.8% to 80%), myalgia (33.3% to 100%), objective fever (12.5% to 50%), and subjective fever (29.2% to 80%). Severe solicited systemic events reported by subjects who received ≥2 x 10^7 pfu V920 included: chills, fatigue, headache, myalgia, sweats, and subjective or objective fever. Severe events were

reported at most by one or two subjects per dosing group. The median duration of events after V920 (≥2 x 10^7 pfu) was between 1.0 to 4.0 days, with the exception of a single subject who reported diarrhea which lasted 9 days.

In V920-009, a higher proportion of subjects in the V920 group reported solicited systemic events (61.6%) compared to subjects in the placebo group (56.7%) through Day 28. The following solicited systemic events were the most commonly reported: fatigue (18.5% of V920 recipients compared to 13.4% of placebo recipients), pyrexia (34.3% of V920 recipients compared to 14.8% of placebo recipients), myalgia (32.5% of V920 recipients compared to 22.8% of placebo recipients), and headache (36.9% of V920 recipients compared to 23.2% of placebo recipients). No subject reported severe events.

Reviewer's comment: Fatigue, headache, myalgia, and fever/chills were commonly reported after V920 and were consistently reported by a higher proportion of subjects after V920 compared to placebo. Severe solicited systemic events were observed in a limited number of subjects in the Phase 1 studies. Data on the duration of solicited systemic events was not collected for V920-009. Solicited systemic events in V920-012 included joint and skin-related events which are discussed in Section 8.4.8 (Adverse Events of Special Interest).

Open label studies
In Phase 1 open-label studies, 81.3 to 93.3% of subjects reported any solicited systemic event through Day 14. The following solicited systemic events were the most commonly reported by subjects who received ≥2 x 10^7 pfu V920: fatigue (10% to 55% of subjects), headache (50% to 60% of subjects), myalgia (12.5% to 70% of subjects), and fever/pyrexia (30% to 56.3% of subjects). Grade 3 events of fatigue, and myalgia were reported by single subjects in V920-006. Grade 3 events of chills (n= 1), fatigue (n= 3), and headache (n=3) were reported in V920-008. The median duration of events was between 1.0 and 7.0 days across the studies.

In V920-010, 59.5% of subjects reported any solicited event (including local and systemic) through Day 14. The most commonly reported solicited systemic events included headache (33.5% of subjects), fatigue (26.1% of subjects), muscle pain (18.6% of subjects), and myalgia (18.3% of subjects). Most solicited events were mild to moderate in severity (98.6%). Of the 82 severe solicited events (1.2% of total solicited events), the most frequently reported included fatigue (24% of severe events) and muscle pain/myalgia (22.9% of severe events). The overall median duration of all solicited events was 2 days. The longest median durations of events were observed for severe events, including 7 days for diarrhea and 4 days for vomiting.

In the V920-011 safety sub-study, 91.7% of vaccinated subjects in the Immediate Vaccination group reported any solicited systemic event, compared to 53.7% of unvaccinated subjects in the Deferred Vaccination group through Day 28. The following solicited systemic events were the most commonly reported: headache (76.1% of vaccinated compared to 33.8% of unvaccinated), fatigue (52.7% of vaccinated compared to 14.7% of unvaccinated), feverishness (53.2% of vaccinated compared to 14.3% of unvaccinated), feeling unwell (32.2% of vaccinated compared to 7.8% of unvaccinated), and myalgia (32.2% of vaccinated compared to 6.9% of unvaccinated). Severe solicited systemic adverse events were also more common in vaccinated subjects in the Immediate Vaccination group (3.9% of subjects) compared to unvaccinated subjects in

the Deferred Vaccination group (0.9% of subjects), the majority of which were severe events of elevated temperature occurring within 7 days of vaccination. The proportions of subjects reporting solicited systemic adverse events was highest in the first 7 days following vaccination; in the Day 15 to 28 time period, 34.3% of subjects in the Immediate Vaccination group reported solicited systemic adverse events compared to 19.4% of subjects in the Deferred Vaccination group. The median duration for select solicited systemic events is available for myalgia and fever (2.0 days for vaccinated and unvaccinated).

Reviewer's comment: Findings in the open-label studies were largely supportive of findings in blinded studies for solicited systemic adverse events, with headache, fatigue, myalgia, and fever commonly observed, including infrequent severe manifestations of these symptoms.

Unsolicited adverse events

Blinded studies

Across the Phase 1 blinded studies, the proportions of subjects reporting at least one unsolicited event through Day 28 at doses of 2×10^7 pfu or higher (excluding V920-003) was between 29.2% and 90.0% of V920 recipients and between 43.6% and 88.9% of placebo recipients.

Unsolicited adverse events reported by ≥5% of subjects in more than one study and by more subjects after V920 than placebo included arthralgia (10% to 20.6% of V920 recipients and 0% to 7.7% of placebo recipients) and the following laboratory abnormalities: decreased lymphocyte count (13% to 40% of V920 recipients and 0% to 11% of placebo recipients), decreased white blood cell count (13% to 23% of V920 recipients and 0% to 11% of placebo recipients), decreased neutrophil count (7% to 20% of V920 recipients and 0% of placebo recipients), alanine aminotransferase increased (7% to 10% of V920 recipients and 0% of placebo recipients), and aspartate aminotransferase increased (7% of V920 recipients and 0% of placebo recipients). Grade 3 events reported by more than one subject included lymphopenia and decreased lymphocyte count, all of which were reported in V920-001 and were assessed as vaccine-related. Most of the unsolicited events that were considered vaccine-related were laboratory abnormalities.

Reviewer's comment: Events of arthralgia and arthritis are discussed in detail in Section 8.4.8. The impact of vaccination on white blood cell parameters was noted across the Phase 1 studies. Although decreases in white blood cell counts were noted, no clear safety signal of increased susceptibility to infection was noted. Adverse events of transaminase elevations were reported after V920 and not after placebo; however, a full assessment of the impact of vaccination on hepatic enzymes is discussed in Section 8.4.5, comparing laboratory trends between treatment groups, as opposed to adverse events.

In V920-009, the proportions of subjects reporting at least one unsolicited event through Month 1 was 18.2% for V920 recipients and 15.2% for placebo recipients. Decreased appetite (3.8% of V920 recipients compared to 2.4% of placebo recipients) was the only unsolicited event reported by more subjects after V920 compared to placebo and reported by more than 2% of subjects. The unsolicited events reported in this study were mild to moderate in severity.

Reviewer's comment: It is unclear why the reporting rate of unsolicited events was lower in V920-009 compared to other studies.

In V920-012, the proportions of subjects reporting at least one unsolicited event, including SAEs, was 52.2% for the Combined Lots group, 58.1% of subjects in the High Dose lot group and 30.8% for the placebo group through Day 42. Unsolicited adverse events reported by ≥5% of subjects in the Combined Lots group and by more subjects after V920 than placebo included nausea (5.1% in Combined Lots group, 5.4% in the High Dose group, and 0.8% in placebo group), chills (6.3% in Combined Lots group, 10.4% in the High Dose group, and 0.8% in placebo group), fatigue (5.7% in Combined Lots group, 7.7% in the High Dose group, and 2.3% in placebo group), influenza like illness (5.6% in Combined Lots group, 3.5% in the High Dose group, and 0.8% in placebo group), pain (10.9% in Combined Lots group, 12.7% in the High Dose group and 1.5% in placebo group), myalgia (5.1% in Combined Lots group, 8.8% in the High Dose group and 0.8% in placebo group), and headache (21.1% in Combined Lots group, 25.8% in the High Dose group, and 11.3% in placebo group).

Severe systemic events reported by more than 1% of subjects in the Combined Lots group, the High Dose group or the Placebo group included vomiting (0.3%, 1.2%, and 0% of subjects, respectively), chills (0.8%, 1.2%, and 0% of subjects, respectively), fatigue (0.8%, 1.9%, and 0% of subjects, respectively), influenza like illness (0.9%, 1.2%, and 0% of subjects, respectively), pain (1.1%, 0.8%, and 0% of subjects, respectively), pyrexia (1.5%, 2.3%, and 0% of subjects, respectively), myalgia (0.4%, 1.2%, and 0% of subjects, respectively), dizziness (0.3%, 1.5%, and 0% of subjects, respectively), and headache (3.0%, 3.5%, and 0% of subjects, respectively).

Vaccine-related systemic events (including solicited and unsolicited) were reported by a higher proportion of subjects in the V920 groups (53.0% in the Combined Lots group and 61.2% in the High Dose group) compared to placebo (14.3%). The most frequently reported related unsolicited adverse events were pyrexia and headache. The most frequently reported vaccine-related systemic AEs (>5% in one or more vaccination group) from Days 1 to 42 post-vaccination were pyrexia, headache, arthralgia, chills, and fatigue.

Reviewer comments: V920-012 provides the largest source of data for unsolicited events. The pattern of the most common unsolicited events is consistent with symptoms that may be due to vaccine reactogenicity and were also frequently observed when solicited in Phase 1 studies, such as pain, fatigue, myalgia, and headache. The most commonly reported severe systemic events (>1% of subjects in any group) were exclusively reported after administration of V920, were generally reported more frequently in the High Dose group, and were events that were consistent with systemic reactogenicity due to V920.

Open-label studies
Across the open-label Phase 1 studies, the proportions of subjects reporting at least one unsolicited event was between 52.5% and 83.3% of V920 recipients through Day 28. Unsolicited adverse events reported by ≥5% of subjects in more than one study include back pain (5.2% to 23.3% of subjects), paraesthesia (4.3% to 7.5% of subjects), malaria (5.0% to 7.0% of subjects), dysgeusia (2.6% to 5% of subjects), and cough (7.8% to 10% of subjects). Grade 3 unsolicited AEs included malaise, muscle tightness, and

dysmenorrhea. The majority of unsolicited events in the studies were considered related to vaccination.

In V920-010, 13.3% of subjects reported an unsolicited event through Day 14. No single event was reported by more than 2.3% of subjects, and events reported by ≥1% of subjects included chills (1.7% of subjects), fever (3% of subjects), gastritis (1.8% of subjects), lumbar pain (2.3% of subjects), and vertigo (2.3% of subjects). These events were not graded or assessed for causality.

In the safety sub-study of V920-011, unsolicited events were reported by a higher proportion of all vaccinated subjects in the Immediate Vaccination group (38.0% mild events, 6.8% moderate events, and 4.4% severe events) compared to unvaccinated subjects the Deferred Vaccination group (9.1% mild events, 1.3% moderate events, and 1.3% severe events) through Day 28. The difference between the groups was most pronounced in the first week following vaccination, during which 39.5% of vaccinated subjects in the Immediate Vaccination group reported unsolicited events compared to 3.9% of unvaccinated subjects in the Deferred Vaccination group. Events reported by a higher proportion of vaccinated subjects in the Immediate Vaccination group compared to unvaccinated subjects in the Deferred Vaccination group and by ≥5% of subjects included asthenia (5.9% of vaccinated subjects and 0.9% of unvaccinated subjects) and pain (6.8% of vaccinated subjects and 1.7% of unvaccinated subjects). Of the nine severe events reported by subjects in the Immediate Vaccination group, five were pyrexia. No other severe events were reported by more than one subject.

For the full safety population of V920-011, unsolicited events were reported by 60.3% of vaccinated subjects in the Immediate Vaccination group compared to 23.1% of unvaccinated subjects in the Deferred Vaccination group through Month 6 (randomized portion of study only). The most commonly reported unsolicited events included headache, pain, pyrexia, and arthralgia. Overall, any mild, moderate, and severe unsolicited event was reported by 46.5%, 3.2%, and 0.7% of all vaccinated subjects (n= 7960 including the Deferred-Crossover group). Most individual adverse events were reported by a higher proportion of subjects in the Immediate Vaccination group compared to the Deferred Vaccination group and the Crossover Vaccination group. Among vaccinated subjects, the most frequently reported severe event was pyrexia.

Reviewer's comment: As causality was not assessed for the open-label Phase 2/3 studies, an analysis of events considered related to V920 is not possible. However, a pattern of a higher frequency of unsolicited events consistent with vaccine reactogenicity is noted, including events such as pain, fever, and headache observed across one or more study.

8.4.7 Local Reactogenicity

In V920-012, local adverse events were solicited for 5 days following vaccination. In all remaining studies, local adverse events were solicited for a minimum of 14 days for all subjects or a subset of subjects (V920-011). In V920-009, local adverse events were solicited as pain/tenderness or local reaction, which was defined as erythema or swelling (mild [Grade 1]; moderate [Grade 2]), blistering (severe [Grade 3]), or ulceration or necrosis (potentially life threatening [Grade 4]); therefore, the verbatim term, local reaction, was used for the safety analyses.

Blinded studies

Pain/tenderness was the most commonly reported injection site reaction across the blinded studies. The proportions of subjects reporting injection site reactions is summarized in the following table.

Table 62 Proportions of subjects reporting solicited injection site reactions in blinded studies

Blinded Study	V920 group(s) % of subjects reporting 1 or more solicited injection site AE	Placebo % of subjects reporting 1 or more solicited injection site AE
Combined Phase 1	43.1-86.7	10.6-33
V920-009	34.0	11.2
V920-012*	72.7	15.0

*Combined phase 1 studies include: V920-001, V920-002, V920-003, V920-004, and V920-005.
*Injection site reactions were solicited for Days 1-5; data presented is for the V920 Combined Lots
Source: Original BLA 125690/1; Summary of Clinical Safety, p. 53-57, Table 2.7.4:12

In the Phase 1 blinded studies (14-day post-vaccination time period):

- Pain (captured as injection site pain, arm pain, or local tenderness) was reported by 57.4% to 100% of V920 recipients (doses ≥2 x 10^7 pfu), compared to 7.4% to 33% of placebo recipients.
- Injection site erythema and swelling were reported by 2.4% to 20% and 2.1% to 10% of V920 recipients (doses ≥2 x 10^7 pfu), respectively, and were not reported by placebo recipients.
- Solicited injection site reactions reported by V920 recipients (dose ≥2 x 10^7 pfu) had a median duration between 1 and 8 days compared to 1 to 2 days for placebo recipients. Most events were reported in the first day following vaccination and none of the events were severe.

In V920-009 (28-day post-vaccination time period):

- Injection site pain was reported by 34.0% of V920 recipients and 11.2% of placebo recipients.
- Local reactions were reported by 1.8% of V920 recipients and 0.8% of placebo recipients.
- Most events of injection site pain were reported at the Week 1 visit. By the Month 1 visit, reports of injection site pain were comparable between the V920 (1.6% of subjects) and placebo (1% of subjects) groups. No injection site events were severe.

In V920-012 (5-day post-vaccination time period):

- Injection site pain was reported by 70.0% of V920 recipients in the Combined Lots group and 12.8% of placebo recipients.
- Injection site erythema was reported by 13.4% of V920 recipients in the Combined Lots group and 1.5% of placebo recipients.
- Injection site swelling was reported by 16.6% of V920 recipients in the Combined Lots group and 3.0% of placebo recipients.
- The duration of solicited injection site reactions was between 1 and 6 days. Severe events of injection site pain were reported by 2.8% of subjects in the Combined Lots group. Severe events of injection site erythema and swelling were reported by 0.3% and 0.9% of subjects in the Combined Lots group, respectively.

Reviewer's comment: Across the blinded studies, events of injection site pain were the most commonly reported solicited local event and were consistently reported by a higher proportion of subjects after V920 than placebo. Severe events of injection site pain were infrequently reported.

Open label
In the V920 Phase 1 open-label trials, 30.4% to 75.0% of adult subjects in the V920 Combined Dose groups experienced solicited injection-site reaction through 14 days Post-vaccination. Injection site pain was the most commonly reported solicited injection site reaction. Most events had a time to onset of ≤1 day after vaccination and none were severe.

In V920-010, solicited injection-site reactions were infrequently reported compared to other studies, with 8.8% of adult subjects reporting injection site pain in the 14 days following vaccination. Severe events of injection site pain were reported by 3.9% of vaccinated subjects. The median duration of events of injection site pain was 2 days.

In V920-011, solicited local adverse events were only collected for vaccinated safety sub-study subjects in the Immediate Vaccination group, 80% of who reported any local solicited event. Between Days 0 to 7, 81% of subjects reported injection site pain, 0.9% reported redness, and 2.8% reported swelling. Most of the events were mild, none of the events were severe, and most subjects reported the events between Days 0 to 4 after vaccination.

Reviewer's comment: The local solicited event findings in the open-label studies were generally consistent with findings in the blinded studies. V920-010 had low reporting rates for injection site pain, which may be attributable to numerous differences between the design and context of this study compared to all other studies in the clinical development program.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

All of the Phase 1 studies assessed multiple doses of V920. Additionally, a High Dose (1 x 10^8 pfu/dose) treatment arm was included in V920-012.

In most studies, a dose-dependent relationship was observed for local injection site reactions. In some studies, a dose-dependent relationship was observed for certain solicited systemic events; the specific dose-dependent systemic events varied by study and included chills, fever, sweats, fatigue, pain, myalgias, headache, and arthralgia. Events of arthritis were not noted to be dose-dependent. There was no pattern of unsolicited events to suggest a safety signal at higher doses of V920.

In two Phase 1 studies, leukocyte decreases were observed in a higher proportion of subjects in the highest dose cohorts, although other hematologic findings were comparable across dosing groups.

8.5.2 Time Dependency for Adverse Events

N/A

8.5.3 Product-Demographic Interactions

N/A

8.5.4 Product-Disease Interactions

N/A

8.5.5 Product-Product Interactions

Effectiveness of V920 when administered concurrently with antiviral medication, immune globulin (IG), and/or blood or plasma transfusions is unknown.

8.5.6 Human Carcinogenicity

N/A

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

N/A

8.5.8 Immunogenicity (Safety)

N/A

8.5.9 Person-to-Person Transmission, Shedding

In the Phase 1 studies, subjects were assessed for vaccine viremia and viral shedding of V920 using RT-PCR assays. The time points for PCR testing varied by study and the RT-PCR assays were conducted by different laboratories with different assay methods. The V920 Phase 2 and 3 studies did not assess vaccine viremia and viral shedding. Viral shedding was not assessed in V920-008.

<u>Vaccine viremia</u>
Vaccine viremia was assessed via RT-PCR in the Phase 1 studies and in a very limited number of subjects in V920-009. In the Phase 1 studies, viremia was assessed through seven days post-vaccination in four studies, through 14 days in two studies, and through 28 days in two studies.

- In studies V920-001, V920-002, V920-005, V920-006, V920-007, and V920-008, 100% of subjects who received a dose of 2×10^7 pfu or higher had detectable vaccine viremia at some point after vaccination. At Day 7, between 0% to 30.0% of subjects in each dose group were viremic. Viremia was not detected in any subject at Days 14 or 28.
- In V920-003, which assessed doses that were lower than 2×10^7 pfu, the proportion of subjects with vaccine viremia at any time point was 90% in the 3×10^6 pfu group and 50% in the lower dose groups. Viremia was not detected in any subject at Days 7 or 14.
- In V920-004, the proportion of subjects with vaccine viremia at any time point was much lower than other studies, even at higher doses. In the 2×10^7 and 1×10^8 pfu dose groups, 21.7% and 62.2% of subjects had detectable vaccine viremia at any time point, respectively, and no vaccine viremia was detected after

Day 3 in these groups. One subject in the 3 x 10^6 pfu dose group had detectable viremia at Day 14.

- In V920-009, of the eight vaccinated subjects who participated in a sub-study to measure plasma levels of V920 RNA, RNA was detected in the plasma of two subjects (25%). One subject had V920 RNA on Day 3 but not on Days 10 and 14, whereas the results in the second subject were positive on Days 3 and 10 but not on Day 14.

In all studies, the latest time point at which viremia was detected was Day 14.

Viral shedding

Viral shedding in the saliva and urine was assessed via RT-PCR in seven Phase 1 studies. Shedding was assessed though three days post-vaccination in one study, seven days post-vaccination in two studies, though 14 days post-vaccination in two studies, and through 28 days post-vaccination in two studies.

Urine

- In studies V920-001, V920-002, V920-004, V920-006, and V920-007, none of the subjects who received a dose of 2 x 10^7 pfu or higher had vaccine virus detected in the urine at any time point after vaccination.
- In V920-003, which assessed doses that were lower than 2 x 10^7 pfu, no subjects had vaccine virus detected in the urine at any time point after vaccination.
- In V920-005, 41 subjects had urine testing completed and detectable but not quantifiable V920 was present in five subjects on Day 1 and five subjects on Day 3.

Saliva

- In studies V920-001, V920-002, V920-004, V920-006, and V920-007, 0% to 40% of subjects who received a dose of 2 x 10^7 pfu or higher had vaccine virus detected in the saliva at any time point after vaccination.
- In V920-001, one subject had vaccine virus RNA detected in the saliva at Day 14.
- In V920-003, which assessed doses that were lower than 2 x 10^7 pfu, no subjects had vaccine virus detected in the saliva at any time point after vaccination.
- In V920-005, 41 subjects had saliva testing completed and detectable but not quantifiable V920 was present in five subjects on Day 1 and 5 subjects on Day 3.

8.4.8 Adverse Events of Special Interest

Arthralgia/arthritis

Blinded studies

After the observation of events of arthritis in V920-005, routine solicitation for joint-related events was added to the clinical development program and was collected for the following double-blind, placebo-controlled studies: V920-004, V920-005, V920-009, and V920-010. However, the specific events and clinical evaluation of arthritis varied between the studies, as summarized in the following table:

Table 63 Case definition and solicited terms for arthralgia and arthritis in blinded clinical studies

	Case definition	Solicited terms
V920-004	Arthritis was defined as: Cohort 1: a joint-related AE Cohort 2: (1) a joint-related AE and (2) a finding of arthritis, defined as a reduction in range of motion, synovitis (tenderness or swelling), or effusion, that are both present between Days 5 and 56 following vaccination with V920	Arthralgia and arthritis (joint aches/pain [general or while moving joints] or joint swelling) and location of joints using memory aid for Days 1-14 (Cohort 1) and Days 1-52 (Cohort 2; arthritis only)
V920-005	Arthralgia with swelling noted upon clinical exam by the investigator/study team, or if imaging (ultrasound or magnetic resonance imaging) showed joint effusion(s), or both. Index (initial) arthritis AEs were defined using the single solicited AE term of "arthritis", and recurrent arthritis AEs were defined using solicited AE terms arthritis or arthralgia reported after the date of the initial arthritis case	Arthralgia and arthritis collected using memory aid for Days 1-14
V920-009	None	Joint problems (pain/tenderness, swelling, stiffness, redness/warmth) at Week 1, Week 2 (sub-study), and Month 1 (no memory aid)
V920-012	Composite term of arthritis for analysis: arthritis, monoarthritis, polyarthritis, osteoarthritis, joint swelling, or joint effusion. The pre-specified assessment of AEs of arthritis was conducted from Days 5 to 42	Arthralgia (joint pain) and/or arthritis (joint pain along with 2 or more of the following symptoms: joint swelling, stiffness, erythema, warmth, tenderness, limitations of range of motion, and/or effusions) using memory aid from Days 1-42

Source: Original BLA 125690/1; CSRs for V920-004, V920-005, V920-009, and V920-012

Arthralgia:
In the Phase 1 blinded studies, solicited events of arthralgia were reported by a higher proportion of subjects after any dose of V920 (10% to 50% of subjects) compared to placebo (0% to 22% of subjects).
In V920-009, solicited events of arthralgia were reported by a slightly higher proportion of subjects after V920 (7.0% subjects) compared to placebo (5.8% of subjects) through Month 1.
In V920-012, solicited events of arthralgia were reported by a higher proportion of subjects in the Combined Lots and High Dose group (17.1% and 20.4% of subjects, respectively) compared to placebo (3.0% of subjects) from Days 1 to 42. In an analysis of events of arthralgia with onset from Days 5 to 42, solicited events of arthralgia were reported by a higher proportion of subjects in the Combined Lots and High Dose groups (5.9% and 7.7% of subjects, respectively) compared to placebo (3.0% of subjects). Severe events of arthralgia were reported by 0.8% and 3.1% of subjects in the Combined Lots and High Dose groups, respectively, and were not reported after placebo.

Arthritis:
In V920-001 and V920-002, events of arthritis were not solicited or reported. In V920-003, events of arthritis were not solicited, but a single subject reported unilateral knee swelling with onset 13 days after vaccination that was graded as mild and resolved within 2 weeks.

In V920-004, temporally-associated arthritis was reported by 4.5% of all V920 recipients and 3.2% of placebo recipients. Between 4.7% to 6.3% of subjects in each dose group

of Cohort 1 (lower dose groups) reported arthritis, compared to 1.4% of subjects in the placebo group (Days 1 to 14). The median time to onset was between 8 and 14 days after V920 and 6 days after placebo. The median duration was between 8 to 19 days after V920 and 47 days after placebo. In Cohort 2 (higher dose groups), between 2.1% to 5.0% of subjects in each dose group reported arthritis, compared to 10% of subjects in the placebo group (Days 1 to 56). The median time to onset was between 12 and 17 days after V920 and 17.5 days after placebo. The median duration was between 3 to 7 days after V920 and 118 days after placebo. All cases of post-vaccination arthritis resolved in subjects vaccinated with V920, although one subject reported a recurrence of arthritis 2 days after the end date of her initial episode of post-vaccination arthritis.

Reviewer comments: In Cohort 2 of V920-004, arthritis data were solicited for a longer duration and in conjunction with specialist input, and the proportion of subjects reporting arthritis was lower after V920 than after placebo. No dose-dependent relationship to vaccination was noted.

In V920-005, events of arthritis were reported by a high proportion of subjects after V920 (23.5%) and were not reported after placebo. Of the 24 subjects with arthritis, 12 were graded as severe. Ongoing symptoms were reported up to 1 year after vaccination in 12 subjects and up to 2 years after vaccination in six subjects. Recurrent symptoms were reported by five subjects. The total media duration of events was 81.5 days. Synovial fluid was obtained from three subjects for a RT-PCR assay for vaccine virus, which was positive for all three subjects, including two subjects at Days 14 and 20 post-vaccination and one subject positive at Day 14 post-vaccination.

In V920-009, events of arthropathy and joint swelling were infrequent but were more common after V920 (0.6% and 0.2% of subjects, respectively) compared to placebo (0.2% and 0% of subjects, respectively). At Week 2, events of arthralgia were reported by 2% of subjects in the V920 group and 4% of subjects in the placebo group. By Month 1, the proportions of subjects reporting joint symptoms was comparable between the V920 group (7.0%) and the placebo group (5.8%), including the subset data from Week 2.

In V920-012, solicited events of arthritis were reported only in the Combined Lots and High Dose groups (4.9% and 4.6% of subjects, respectively) and were not reported after placebo. Severe events of arthritis were reported by 0.6% and 1.2% of subjects in the Combined Lots and High Dose groups, respectively. In an analysis of events of arthritis with onset from Day 5 to 42 post-vaccination, only in the Combined Lots and High Dose groups (3.7% and 3.1% of subjects, respectively) and were not reported after placebo. Across the Combined Lots and High Dose groups, the median time to onset and duration were 2.0 and 5.0 to 6.0 days, respectively, compared to 5.5 days in the placebo group (Days 1-42). Synovial fluid was obtained from three subjects for a RT-PCR assay for vaccine virus, which was positive for one subject at Day 17.

Reviewer's comment: In V920-005, events of arthritis after V920 were more frequent, persistent, and severe compared to all other blinded studies. Further support for the relationship of these events to V920 includes the presence of vaccine virus RNA in the synovial fluid, although it is unclear whether this represents actively replicating virus. Although the proportions of subjects reporting joint events were generally comparable between the V920 and placebo groups in V920-009, events of arthritis were only observed after V920 in V920-012 and were associated with the presence of vaccine

virus RNA for a single tested subject. It remains unclear why the findings associated with arthritis in V920-005 were different than those observed in larger studies.

Open label studies
In V920-006, solicited events of arthralgia were reported by 16.7% of subjects after V920, including one subject with a Grade 3 event. An unsolicited event of Grade 2 arthritis was reported by one of the 30 vaccinated subjects at Day 20 after V920. In V920-007, solicited events of arthralgia were reported by 14.8% of subjects after V920; unsolicited events of arthralgia were reported by seven of the 115 vaccinated subjects after the 14-day solicitation period. Arthritis was not reported. In V920-008, solicited events of arthralgia were reported by 12.5% of subjects after V920 and a solicited event of Grade 2 arthritis was reported by one of the 40 vaccinated subjects at Day 9 after V920.

In V920-010, solicited events of arthralgia were reported by 18.5% of vaccinated subjects. Events of arthritis were not solicited or reported in V920-010.

In V920-011, solicited events of joint pain were reported in the safety sub-study by a higher proportion of vaccinated subjects (39%) than unvaccinated subjects (9.1%), including one vaccinated subject with a severe event of joint pain reported between Days 15 to 21. Solicited events of joint swelling were also reported in the safety sub-study by a higher proportion of vaccinated subjects (3.4%) than unvaccinated subjects (0.9%), none of which were severe and most of which were reported Days 0 to 7. In the overall population of the V920-011 trial, arthritis was reported infrequently in the Immediate Vaccination group (0.2% of subjects), the Deferred Vaccination group (prior to vaccination; 0.1%), and the Deferred-Crossover group (after vaccination; 0.1%), all of which were mild.

Reviewer's comment: In the larger open-label studies, events of arthritis were infrequent; although the proportions of subjects reporting arthritis in the safety sub-study of V920-011 were comparable to findings in V920-012.

<u>Skin and mucosal events</u>
Blinded studies
In the Phase 1 blinded studies, skin and mucosal events were not solicited or reported in V920-001, V920-002, and V920-003, with the exception of rare reports of contact dermatitis and oral ulcer. In V920-004, events of mouth ulcers and skin lesions were solicited for 14 days for subjects in Cohort 1 (lower dose groups) and for 56 days for subjects in Cohort 2 (higher dose groups). Post-vaccination dermatitis was defined as: a solicited AE term of mucosal lesions or skin lesions, or an unsolicited AE preferred term of dermatitis, petechiae, pityriasis lichenoides et varioliformis acuta, purpura, rash, rash generalized, rash macular, rash papular, rash vesicular, skin lesion, skin mass, or skin ulcer with onset within 56 days of vaccination. In V920-005, skin and mucosal events were defined by the solicited term of skin lesions and unsolicited terms of rash (including erythematous, generalized, macular, maculo-papular, papular, and vesicular rash), mouth ulceration, papule, and cutaneous vasculitis. After a review of blinded safety data, the composite term of rash was defined as including any of the following: petechiae, purpura, rash, rash generalized, rash macular, rash papular, and rash vesicular. This composite term was also used in V920-012.

In V920-004, 5.7% of subjects in the V920 groups reported events meeting the definition of dermatitis, compared to 3.2% of subjects in the placebo groups. No clear dose-dependent relationship was identified. The median time to onset and duration were 9.0 and 7.0, respectively, in the V920 groups and 5.0 and 54.0, respectively, in the placebo group. No severe events were reported. Punch biopsy or wound swabs were obtained from nine subjects for RT-PCR to detect vaccine virus RNA, all of which were negative. Mouth ulcers were reported by 1.5% of subjects after V920 and 1.1% of subjects after placebo.

In V920-005, skin and mucosal events were reported by similar proportions of subjects after V920 (29.4%) compared to placebo (30.8%) at any time point post-vaccination. Skin-related events were reported 11.4% and 18.8% of subjects in each of the dose groups and by 17.6% of subjects overall, compared to 7.7% of placebo recipients. Skin-related AEs included cutaneous vasculitis, papule, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash vesicular, and skin lesion. Events of blister were not included in the analysis of skin-related events and were reported by 8.8% of V920 recipients (n= 9) overall. Mouth ulcerations were reported by 15.7% of V920 recipients and 23.1% of placebo recipients. External experts reviewed clinical and histopathologic data from the reports of cutaneous vasculitis and determined that the evidence supported and etiology of hypersensitivity reaction and postviral exanthem, respectively. No severe events were reported. The median time to onset and duration were 8.0 and 10.5, respectively, in the V920 groups and 8.5 and 11.0, respectively, in the placebo group. A total of eight skin samples from five subjects with vesicular lesions were positive for the presence of vaccine virus RNA by RT-PCR, including 3 subjects with skin samples that were positive for V920 on Day 7, Day 14, and Day 14, a subject with two samples positive on Day 7 and two samples positive on Day 14, and a subject with a sample that was positive on Day 20.

In V920-009, comparable proportions of subjects reported solicited events of rash and mouth ulcers in the V920 groups (3.6% and 2.6%, respectively) and the placebo groups (3.2% and 2.6%, respectively) between Days 1 to 14. All events were mild. In V920-012, 3.8% of subjects in the Combined Lots group and the High Dose group reported a solicited event included in the composite term of rash compared to 1.5% of subjects in the placebo group between Days 1 to 42. In both the Combined Lots group and the High Dose group, 1.5% of subjects reported vesicular lesions, which were not reported in the placebo group. No severe events were reported. The median time to onset of rash was 7.5, 10.5, and 3.5 days post-vaccination for the Combined Lots, High Dose, and placebo groups, respectively and the median duration of rash was 6.0, 18.0, and 14.0 days for the Combined Lots, High Dose, and placebo groups, respectively. A total of six subjects underwent RT-PCR testing for vaccine virus RNA of skin lesions; positive results were obtained for one subject with dermatitis on Day 6. A total of five subjects underwent RT-PCR testing for vaccine virus RNA of vesicular fluid; positive results were obtained for one subject with a blister on Day 12.

Reviewer's comment: Across the four blinded studies that provide the most data for skin and mucosal lesions, the proportions of subjects reporting events were generally comparable between the V920 and placebo groups, although vesicular lesions were observed only after V920 in V920-012. The presence of vaccine virus RNA in some of the skin lesions is a potential safety concern as, if the RNA represents replicating virus, V920 could potentially be transmitted to close contacts of vaccinees who come into

contact with vesicular fluid. Additional information on potential transmission of vaccine virus is described in Section 8.5.9.

Open label studies
Events of rash or vesicular lesions were reported by two subjects in V920-006 (6.6%), both of whom had blisters in the mouth and lip, respectively, 1.7% of subjects in V920-007, and one subject in V920-008 (2.5%). Events of rash were not solicited or reported in V920-010. In V920-011, a higher proportion of vaccinated reported events of rash, skin vesicles, and oral ulcers (7.8%, 2.9%, and 0.3%, respectively) compared to unvaccinated subjects (1.7%, 0.9%, and 0%, respectively). No severe events were reported.

Neurologic events
Reviewer's comment: As neurovirulence is observed with wild type VSV, a theoretical risk is that the vaccine virus would demonstrate some neurovirulence despite replacement of the glycoprotein thought to mediate neurovirulence. No pattern of adverse events was observed in any single study or in the ISS to suggest neurovirulence. Events of encephalitis (n= 1), aphasia (n= 2), and loss of consciousness (n= 2) were reported in V920-011, these events are discussed in detail in the individual review of this study (Section 6.4).

Neurovascular and thrombotic events after V920
In the blinded and open label studies, a total of eight neurovascular and thrombotic events were reported after V920, all of which were not considered related to V920 by the Investigator. These events are summarized in the following table.

Table 64 Neurovascular and thrombotic events reported after V920

Study	Age/ Gender	MedDRA Preferred Term	Description of event	Time to onset (Days)	Outcome
V920-009	48/F	Cerebrovascular accident	Symptoms of confusion, left sided hemiplegia, slurred speech, and left facial droop after a fall at home. In the emergency room, blood pressure was 200/130. She had no reported previous history of hypertension and concomitant mediations were not reported.	128	Recovered/ resolved with sequelae
V920-009	61/F	Cerebrovascular accident	Symptoms of left arm and leg weakness and slurred speech with history of hypertension. She presented with. In the hospital, blood pressure was 210/110. Concomitant medications included atenolol and hydrochlorothiazide, with which she was not compliant.	334	Recovered/ resolved with sequelae
V920-011	52/F	Cerebrovascular accident	Symptoms of right hemiplegia, aphasia, fever, night sweats, breathing problems and wheezing, and severe headache. Death occurred 6 days after onset.	56	Fatal

Study	Age/ Gender	MedDRA Preferred Term	Description of event	Time to onset (Days)	Outcome
V920-011	57/M	Hemorrhagic stroke	Symptoms of loss of consciousness and hyperglycemia (234 mg/dL) with a history of diabetes and hypertension, including a previous episode of hypertensive crisis. In the hospital, blood pressure was 200/80 mmHg. Death occurred 1 day after onset. Malaria testing was positive, subject was asymptomatic.	73	Fatal
V920-011	53/F	Subarachnoid hemorrhage	Symptoms of severe headache with a history of hypertension. She was not hospitalized prior to her death, which occurred 3 days after onset. Subarachnoid hemorrhage was diagnosed, although no diagnostic information was provided.	145	Fatal
V920-011	39/F	Cerebrovascular accident (non-serious)	Symptoms of slurred speech and right sided weakness with a history of hypertension. In the hospital, blood pressure was 200/120 mmHg.	77	Not provided
V920-012	49/M	Pulmonary embolism	Symptoms of chest pain and shortness of breath, with a history of overweight and hypertension.	22	Recovered/ resolved
V920-012	33/F	Pulmonary embolism	Symptoms of shortness of breath and chest pain. Concomitant therapies included etonogestrel implant, ethinyl estradiol, and norethindrone acetate. Family history of clotting disorder.	86	Recovered/ resolved with sequelae

F= female; M= male
Source: Original BLA: 125690/1; CSRs for V920-009, V920-011, V920-012

Reviewer's comment: Other events not included in the table that did not clearly represent neurovascular or thrombotic events included two reports of isolated aphasia in V920-011 that spontaneously resolved and a deep vein thrombosis that was due to an upper extremity peripherally inserted central catheter in V920-012.

Events of pulmonary embolism and cerebrovascular accident were reported by two subjects each following V920 and were not reported after placebo. The two events of pulmonary embolism were reported in V920-012 at Days 33 and 86 after V920, respectively, in subjects with underlying medical history that provides potential alternative etiologies for the events, including obesity and hypertension as well as clotting disorder and oral contraceptive use, respectively. The two events of cerebrovascular accident were reported in V920-009 at Days 128 and 334 after V920, respectively, in subjects with severe hypertension at the time of diagnosis (systolic blood pressure ≥200 mmHg). It is possible that an immune response to V920 potentiated an underlying risk of a thrombotic event for these subjects, although the events of stroke were temporally distant from vaccination. However, a full assessment of these events is confounded by a lack of details about the nature of the specific cerebrovascular insult (e.g., whether the event was thrombotic or hemorrhagic). The pattern of events is notable, but no clear conclusion about the relationship of these events to V920 can be drawn. Continued monitoring of neurovascular and thrombotic events through routine pharmacovigilance is recommended.

8.6 Safety Conclusions

Local and/or general solicited symptoms, including infrequent severe manifestations of general solicited symptoms were reported by a higher proportion of subjects after V920 compared to placebo. Overall, deaths and SAEs were reported in similar proportions of subjects in the V920 and placebo groups in the pooled analysis. Related SAEs of anaphylaxis were reported by two subjects. Decreases in leukocyte, lymphocyte, and neutrophil counts were observed shortly after administration of V920 which recovered in subsequent follow up. Routine pharmacovigilance will surveil for pregnancy outcomes, events of arthritis, neurovascular events, and other rare adverse events.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

In the clinical development program, pregnancies were reported in six studies. Most pregnancies were reported in V920-011.

- In V920-004, two pregnancies were reported:
  - A 20-year old female in the 3 x 10^6 dose group had a positive pregnancy test on Day 28 after vaccination, after which she voluntarily terminated her pregnancy,
  - A 20-year old female in the 9 x 10^6 pfu dose group was reported to be pregnant approximately 80 days after vaccination (LMP not reported) and gave birth to a normal male infant at term.
- In V920-007, three pregnancies were reported. Three pregnancies were reported during the trial and were monitored until delivery. No safety complications were reported. No information on the LMP relative to vaccination or treatment arm assignment was provided.
- In V920-008, one pregnancy was reported. A 33-year old female was reported to be pregnant at her 1 year final visit. The pregnancy was followed to the live birth of an infant with no noted congenital anomalies. No information on the LMP relative to vaccination or treatment arm assignment was provided.
- In V920-009, eight subjects who reported being pregnant in the first 30 days after vaccination were followed.
  - Six pregnancies were reported in placebo recipients. Outcomes for these pregnancies include abortion incomplete (n= 1), abortion spontaneous (n= 1), and live birth (n= 4).
  - A 28-year old female received V920 and reported an LMP 29 days after vaccination. At approximately 21 weeks gestation, the subject reported symptoms of malaria associated with vaginal bleeding, although rapid diagnostic testing for malaria was negative. One week later, the subject reported no fetal movement. Ultrasound revealed 22 weeks gestation, no fetal heart rate, and no fetal movement and a diagnosis of intra-uterine fetal demise was made. A blood smear was positive for *P. falciparum* at that time.
  - A 22-year old female received V920 and approximately 11 months later delivered a stillborn infant at home. The case narrative indicates that the labor was difficult but additional details were not provided.

- In V920-012, five pregnancies with an LMP through the Month 6 period were reported.
    - A 30-year old female in the V920 Lot C group with a history of dysmenorrhea and prior spontaneous abortion reported an SAE of spontaneous abortion at Week 4 of pregnancy 35 days after vaccination. The subject did not see a medical provider for the positive pregnancy test or for the spontaneous abortion.
    - A 26-year old female in the V920 Lot A group became pregnant with an LMP 6 days after vaccination. A female infant was delivered via spontaneous vaginal delivery at 36 weeks gestational age.
    - A 27-year old female in the V920 Lot B group became pregnant with an LMP 37 days after vaccination. A full-term female infant was delivered via vaginal delivery.
    - A 22-year old female in the V920 Lot A group was vaccinated on (b) (6) , with an LMP reported in (b) (6) . On an unknown date in 2015, the pregnancy was confirmed by a positive pregnancy test. An estimated delivery date was reported as (b) (6) . This subject was lost to follow-up.
    - A 43-year old in the V920 Lot B group became pregnant with an LMP 11 days prior to vaccination. The estimated date delivery was reported as (b) (6) . The outcome of the pregnancy is unknown.

Reviewer's comment: Details on pregnancies in V920-011 are reviewed extensively in Section 6.4.12.5 (Adverse Events of Special Interest). Pregnancy data from V920-010 were not available to the Applicant for submission to the BLA and therefore could not be reviewed.

The limited number of pregnancies reported in individual studies other than V920-011 preclude a full assessment of the impact of V920. No pattern of pregnancy outcomes was noted in these cases. As discussed in detail in Section 6.4.12.5, interpretation of the pregnancy outcome data from V920-011 is confounded by missing data and the open-label study design, which may have biased reporting. In summary, the available data from clinical trials of V920 are insufficient to establish the presence of absence of vaccine-associated risk during pregnancy.

9.1.2 Use During Lactation

Data on use of V920 in lactating subjects was not provided in the BLA.

9.1.3 Pediatric Use and PREA Considerations

This submission is subject to the Pediatric Research Equity Act (PREA)FDA's Pediatric Review Committee (PeRC) and CBER agreed with the Applicant's request for a waiver of pediatric assessments for children from birth through 11 months of age as the studies are impossible or highly impracticable (e.g. the number of pediatric patients is so small or is geographically dispersed) (section 505B(a)(5)(B)(i)). PeRC agreed with the Applicant's request for a deferral of the pediatric assessment for children 12 months through 17 years of age as the drug or biological product is ready for approval for use in adults before pediatric studies are complete (section 505B(a)(4)(A)(i)(I)).

The deferred pediatric study, Study V920-016 to evaluate the safety and immunogenicity of ERVEBO in children 12 months through 17 years of age, is a required study under

PREA. The study is ongoing. The timeline for study completion and final report submission is January 31, 2020 and June 30, 2021, respectively.9.1.4 Immunocompromised Patients
Systematic assessment of analysis of immunocompromised subjects was limited to 22 HIV-infected subjects enrolled in Study V920-009.

Reviewer comments: While it is possible that subjects with undiagnosed or unreported HIV were enrolled in the larger open-label studies, HIV testing was not conducted, and data were not systematically collected. See the review of V920-009 in Section 6.2 for the full evaluation of safety and immunogenicity in HIV positive subjects.

9.1.5 Geriatric Use

In the Phase 1 studies, all subjects were < 65 years of age. In the Phase 2/3 studies, a total of 596 subjects ≥65 years of age were enrolled, including 17 subjects in V920-009, 538 subjects in V920-010, 30 subjects in V920-011, and 11 subjects in V920-012. Of these 585 subjects, 542 received V920, including six subjects in V920-009, 497 subjects in V920-010, 29 subjects in V920-011, and 10 subjects in V920-012.

A subgroup analysis by age was performed only for subjects >55 years of age in the V920-010 ring vaccination study, which demonstrated 100% efficacy (95% CI: 41.2, 100).

Blinded, placebo-controlled safety data for geriatric subjects is available from a limited number of subjects in V920-009 and V920-12.

Reviewer's comment: Safety data for subjects ≥65 years and older is reviewed in Section 1.1 (Demographic Information: Subgroup Demographics and Analysis Summary) and in the individual study reviews (Sections 6.2 and 6.3). No major differences in the safety profile were apparent, although there are very limited data on geriatric subjects in blinded, controlled clinical studies, precluding a comprehensive analysis of safety in this age group.

Of the 497 vaccinated subjects ≥65 years of age in V920-010, SAEs were reported by nine subjects (1.8%), including six reports of EVD, two reports of sudden death, and one report of anaphylaxis. Of these SAEs, the event of anaphylaxis was considered related. Any solicited systemic event was reported by 222 vaccinated subjects ≥65 years of age (44.7%) compared to 59.5% of all vaccinated adults reporting any solicited adverse event.

Solicited events were reported by a lower proportion of subjects ≥65 years of age compared to placebo. The proportions of subjects reporting solicited events at least once are as follows: arthralgia (18.7% of geriatric subjects compared to 18.5% of vaccinated adults), diarrhea (0.4% of geriatric subjects compared to 1.4% of vaccinated adults), fatigue (18.9% of geriatric subjects compared to 26.1% of vaccinated adults), headache (23.5% of geriatric subjects compared to 33.5% of vaccinated adults), myalgia and muscle pain (11.3% of geriatric subjects each compared to 17.3% and 18.6% of vaccinated adults, respectively), and injection site pain (5.2% of geriatric subjects compared to 8.8% of vaccinated adults). The pattern of unsolicited events reported by subjects ≥65 years of age was generally comparable to the overall adult population.

*Reviewer's comment: The safety profile of V920 in subjects ≥65 years of age in V920-010 appears comparable to the overall safety profile in all adults***.**

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

A 4-month development safety update report was submitted to the BLA to provide safety data from ongoing studies. The safety update report includes data through March 29, 2019 from 1 ongoing open label Phase 2 study (V920-013 [study in subjects at occupational risk for Ebola in the US and Canada; exposure n= 129]), 2 ongoing blinded Phase 2 studies (V920-015 [study in HIV-infected subjects in Canada, Burkina Faso, and Senegal; exposure n= 67 including placebo)] and V920-016 [study in children <1 year of age and adults in Guinea, Liberia, Mail, and Sierra Leone; exposure n= 4789 including placebo]), and two Expanded Access Protocols initiated by the WHO in 2018 as part of a public health response to an Ebola outbreak in the DRC (V920-EAP4 [Equateur province; completed; n= 3,481]) and V920-EAP5 [North Kivu, Rwanda, South Sudan, Uganda; ongoing; n= 93,206]). At the time of the data cutoff date for the safety update, 3,481 subjects received V920 in V920-EAP4 and 93,206 subjects received V920 in V920-EAP5. The following data was included in the safety update: vaccine-related SAEs and SAEs resulting in death or discontinuation in V920-013, V920-015, V920-016, V920 EAP4, and EAP5; SAEs reported for HIV-positive adults and adolescents in V920-015, SAEs reported for pediatric subjects in the V920-015, V920-016, V920 EAP4, and EAP5; events of Ebola disease reported for all subjects in V920 EAP4 and EAP5; and SAEs in pregnant female subjects in the V920-013, V920-015, V920-016, and V920 EAP4, and EAP5.

<u>Vaccine-related SAEs and SAEs resulting in death or discontinuation</u>

Deaths
In V920-016, of the 4789 subjects exposed to blinded study vaccine, seven (0.1%) had fatal SAEs reported, including an adult subject with sepsis; a pediatric subject with SAEs of malaria, gastritis, and death (due to unknown cause); two pediatric subjects with death due to unknown cause, and three pediatric subjects with one SAE each of multiple injuries, drowning, and disease complication (presumed meningitis on Day 52 post-vaccination). Of the three pediatric subjects with death due to an unknown cause:

- A 17-year old male had symptoms of prostration, vomiting, headaches, fever, epigastric pain, and anorexia and was diagnosed with malaria and gastritis on Day 372 post-vaccination and was hospitalized on Day 375. The subject was discharged from the hospital against medical advice and subsequently died on Day 377 post-vaccination.
- A 4-year old female developed a fever and altered consciousness on Day 163 post-vaccination and died of an unknown cause at home on Day 165 post-vaccination.
- A 13-year old male reported symptoms of dizziness prior to being taken to a healthcare center where he died suddenly of an unknown cause on Day 220 post-vaccination.

In the expanded access protocols, 10 subjects reported fatal SAEs, including eight events of EVD. Additional fatal SAEs included:

- A 15-year old female was reported to have an event of acute respiratory distress syndrome 4 days after vaccination. She had acute respiratory distress syndrome with headache, epigastric pain, and cough and was admitted to a health center where she was noted to be dehydrated. The following day, she had worsening dyspnea, chest pain, and sweating. On Day 6 after vaccination, her clinical status worsened and she died. An Ebola swab was negative.
- Events of prematurity, exposure during pregnancy, and neonatal aspiration were reported for a newborn infant who was born at 28.5 weeks gestational age 11 days after the mother was vaccinated with V920. At 18 days of age, the infant was noted to have an aspiration event and subsequently developed respiratory failure and died.

None of the SAEs resulting in death were considered related to study vaccine by the investigator.

Reviewer's comment: A full assessment of causality for the two non-EVD related deaths is limited by a lack of diagnostic information. Fatal events of respiratory failure temporally related to vaccine were not reported in the clinical development program.

Discontinuations
No non-fatal SAEs resulted in discontinuation from the V920 ongoing clinical trials or EAPs.

Related SAEs
No SAEs reported for adults in the V920-013 and V920-016 trials were considered related to study vaccine by the investigator.

In the expanded access protocols, a total of 19 adult subjects reported 25 SAEs that were considered vaccine-related or had unknown causality. SAEs of EVD were considered related for 2 subjects and of unknown causality for 12 subjects. The remaining nine related SAEs reported by five subjects included ill-defined disorder; pyrexia; anaphylactic reaction; events of gastrointestinal infection, adverse event, EVD (verbatim term: fear of Ebola) and sepsis reported by a single subject; and events of malaria, multi-organ dysfunction syndrome, mental status changes, and post-procedural complication reported by a single subject.

- The event of anaphylaxis occurred 1 day after V920 and included symptoms of itchy body rash, fever, headache, malaise, and low blood pressure. The subject was treated with hydrocortisone and prednisolone.

Reviewer's comment: Limited information is provided regarding the diagnosis of anaphylaxis. The events occurred on the day following vaccination; however, the duration of the interval between vaccination and the onset of symptoms is not provided. The subject had other symptoms (fever, headache, malaise) that could be attributable to vaccine reactogenicity. Additional information is needed to clarify the timing of onset of symptoms, as onset <24 hours after vaccination could be consistent with anaphylaxis while onset >24 hours may suggest an alternative etiology for the hypotension.

- The events of gastrointestinal infection, adverse event, and EVD (verbatim term: fear of Ebola) were reported by a 24-year old male who reported symptoms of fever and joint pains 6 days after V920. By Day 9 post-vaccination he had symptoms of gastroenteritis, asthenia, anorexia, and dehydration. He was hospitalized and multiple PCR tests for EVD were negative. The subject reported persistent myalgia and worsening joint pain in two knees accompanied by anorexia, asthenia, angina, and dehydration. He was re-hospitalized due to the joint pains associated with nonpurulent rashes. Due to inconsistencies in the case report, the dates of hospitalization and rehospitalization are unclear. The subject was diagnosed with malaria and sepsis and was treated with antibiotics and antimalarial. On an unknown date, the subject was fully recovered with no symptoms/signs of arthritis and the event was closed.

Reviewer's comment: A full assessment of this report is limited due to limited diagnostic information; however, the onset of polyarthritis was temporally related to V920 administration and was accompanied by other symptoms consistent with the known reactogenicity profile of the vaccine. The concurrent diagnosis of malaria may be a plausible alternative etiology for the symptoms; however, limited information regarding the malaria diagnosis are provided and the symptoms appear to persist after treatment.

- The events of malaria, multi-organ dysfunction syndrome, mental status changes, and post-procedural complication were reported by a 42-year old male with a history of Type 2 diabetes mellitus. On the day following vaccination, the subject reported fever, nausea, vomiting, diarrhea, and muscle pain, which resolved after a "few" days. Seven days after vaccination, the symptoms returned, and the patient traveled to the US. The subject was seen by a physician 10 days after vaccination with altered mental status, multiorgan system failure, and was diagnosed with one or two strains of malaria. The patient was hospitalized in the medical intensive care unit for three weeks and received comprehensive treatment. Diagnostic information was not provided with the report; however, Ebola testing was reportedly negative. Complications after the critical illness resulted in the need for rehabilitation. The patient did not recover from all the events.

Reviewer's comment: Malaria infection is a plausible alternative etiology for the reported SAEs; the clinical course of the subject could be consistent with cerebral malaria. Underlying diabetes mellitus may have predisposed the subject to more severe manifestations of malaria.

- The event of illness was reported by a 52-year old female who had symptoms of headache, abdominal pain, jaw pain, and fatigue and was hospitalized the day after vaccination. Her blood pressure was 170/100. She received butylscopolamine bromide, ibuprofen, magnesium and paracetamol and was discharged home after a 2-day hospitalization.
- The event of pyrexia was reported by a 40-year old male 3 days after vaccination, at which time he had headaches, dizziness, asthenia, and a temperature of 38.5º C. He was hospitalized and treated with hydrocortisone, promethazine, and saline.

Reviewer's comment: The symptoms reported in the above two cases are consistent with systemic reactogenicity observed following vaccination; however, it is unclear from the details provided why the complaints necessitated hospitalization.

SAEs reported for HIV-positive adults and adolescents in V920-015

SAEs were not reported in V920-015.

SAEs reported for pediatric subjects in the V920-015, V920-016, V920 EAP4, and EAP5
In V920-016, a total of 31 pediatric subjects reported 39 SAEs. SAEs reported by more than one subject include eight events of appendicitis and four events of malaria. Most SAEs were reported in the Infections and infestations system organ class.

In the expanded access protocols, a total of 18 pediatric subjects reported 21 SAEs. SAEs reported by more than one subject include 13 events of EVD or suspected EVD and 3 events of malaria; other SAEs included anemia, respiratory tract infection, burns second degree, acute respiratory distress syndrome, and asthma. None of the SAEs were considered related to study vaccine by the investigator.

Reviewer's comment: As per PREA (see Section 9.1.3), submission of the CSR for V920-016 is a post-marketing requirement for the Applicant, at which time more complete and unblinded pediatric safety data will be available.

SAEs in pregnant subjects
In V920-013, a pregnant subject experienced an SAE of spontaneous abortion at Day 121 post-vaccination that was considered not related to V920 by the investigator.

In V920-016, SAEs were reported by eight pregnant subjects, including incomplete abortion (n= 2), metrorrhagia (n= 2), abdominal pain, appendicitis, ectopic pregnancy, obstructed labor, and uterine dilatation and curettage. SAEs were reported for two neonates, including a fetal death at Day 388 post-vaccination of a twin at 28 weeks gestational age and an event of fetal distress syndrome in an infant delivered via Caesarean section Day 282 after vaccination (discussed above).

In the expanded access protocols, SAEs were reported by five pregnant subjects, including malaria (n= 2), pelvic infection, abortion induced complete complicated, abortion threatened, and premature delivery. SAEs were reported for one neonate, including prematurity and death due to neonatal aspiration (discussed above).

None of the SAEs reported for pregnant subjects or neonates were considered related to study vaccine by the investigator.

Events of Ebola disease reported for all subjects in V920 EAP4 and EAP5

Breakthrough Ebola disease, defined as laboratory-confirmed Ebola disease (Zaire type) in a study subject with onset ≥10 days post-vaccination, was reported by 21 vaccinated subjects in the expanded access protocols (all in V920-EAP5). Of the 21 subjects, 15 subjects had Ebola disease confirmed with a positive Ebola virus PCR test and thus had confirmed breakthrough Ebola disease. Of the 15 subjects with confirmed breakthrough Ebola disease, 14 recovered and one had an unknown outcome at the time of the data

lock for the safety update report. The time to onset of the cases ranged from 13 to 103 days after vaccination.

Reviewer's comment: In contrast to V920-010, post-vaccination breakthrough cases of EVD are being observed in the ongoing expanded access ring vaccination study in the DRC. Final study data from V920-EAP5 will be a post-marketing commitment for the Applicant, as the estimates of vaccine efficacy and safety data from this study will be informative, given the size of the study. In a preliminary analysis conducted by the DRC's national research institute, the Institut National pour la Recherche Biomedicale and WHO and provided online (https://www.who.int/csr/resources/publications/ebola/ebola-ring-vaccination-results-12-april-2019.pdf), data collected between May 1, 2018 and March 25, 2019, all 15 subjects with onset of EVD symptoms ≥10 days after vaccination were alive. The WHO estimated that Ebola attack rate for vaccinated individuals was about 0.017%, compared with an estimated 0.656% in unvaccinated individuals, yielding an estimated vaccine efficacy of 97.5%, 95% CI [95.8 – 98.5%].

10. CONCLUSIONS

V920 VE was confirmed in V920-010. Considerations in interpretation of the VE data include potential sources of bias associated with the study design and the conduct of a study in an outbreak setting, as well as the narrow analysis window. The durability of protection from EVD was not assessed in this study.

Additional studies submitted to the BLA provided initial assessments of safety and immunogenicity (open-label studies), demonstrated the immunogenicity of V920 at various dose levels and confirmed the lot-to-lot consistency of V920 (V920-012).

In the blinded studies, local and/or general solicited symptoms, generally of short duration, were commonly reported by subjects evaluated in the V920 groups. Severe reactogenicity was reported. Events of arthritis and arthralgia were reported by a higher proportion of subjects after V920 compared to placebo; the detection of vaccine virus RNA in the synovial fluid of some subjects with arthritis suggests an association with V920. Vesicular rash was also present in some vaccinees; the detection of vaccine virus RNA in skin specimens of some subjects with rashes and vesicular lesions suggests an association with V920. Related SAEs included two reports of anaphylaxis, pyrexia, infection, febrile reaction, and influenza-like illness, all of which were reported in V920-010. In the pooled analysis, the proportions of subjects reporting SAEs was comparable between the V920 and placebo groups. Routine pharmacovigilance and a proposed pharmacovigilance plan will surveil for events of arthritis of anaphylaxis, pregnancy outcomes, and other adverse events which may not have been observed given the sample size evaluated in the blinded clinical studies.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 65 Risk Benefit Table

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Zaire Ebola virus 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 Ebolavirus disease (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. • A recent outbreak in Guinea, Liberia, and Sierra Leone resulted in 28,616 cases and 11,310 deaths (2014-2016 outbreak). An ongoing outbreak in the Democratic Republic of Congo has resulted in over 3,000 cases. • Case fatality rates of 25% to 90% have been reported for EVD.	• Ebola virus disease is a serious, life-threatening disease with a high risk of mortality.
Unmet Medical Need	• There is no other drug or biologic approved for prevention or treatment of EVD. • If access to investigational products is unavailable during an epidemic, treatment of EVD is limited to the available supportive care measures.	• There is an unmet medical need for effective prevention of EVD, which is associated with significant morbidity and mortality and has no licensed treatments.
Clinical Benefit	• The efficacy of V920 was assessed in a single clinical study (V920-010). In the primary efficacy analysis (all vaccinated subjects in the immediate group versus all subjects who were eligible and consented at Day 0 in the delayed group for the analysis period of Days 10-31 after randomization), no cases of confirmed EVD were observed in the immediate group (n= 2108; 51 clusters) and a total of 10 confirmed EVD cases (attack rate 0.7%) were observed in 4 rings in the delayed group (n= 1429; 46 clusters), resulting in a vaccine efficacy (VE) of 100% (95% CI: 63.5 to 100%, p=0.0471). The impact of the inherent biases and challenges of conducting a ring vaccination study in the setting of an outbreak on the efficacy data is unknown. • The duration of protection conferred by V920 is unknown as the efficacy analysis was limited to a 21-day period post-vaccination. No cases of EVD were observed >10 days post-vaccination through Day 84; however, this time period was not included in the primary efficacy analysis as there was no comparator group. The need for and timing of a booster dose or re-vaccination is not known. • Supportive immunogenicity data demonstrates persistent humoral antibody responses to 1-year post-vaccination; however, the relationship of humoral immunogenicity measures to clinical vaccine efficacy is unknown. • V920 effectiveness was not evaluated in immunodeficient/immunocompromised individuals. • The efficacy of V920 when co-administered with any vaccine has not been evaluated.	• The point estimate for vaccine efficacy of V920 was 100% in the only efficacy, ring-vaccination trial conducted during the 2014- 2016 EVD outbreak in Guinea. Considerations in interpretation of the VE data include potential sources of bias associated with the study design and the conduct of a study in an outbreak setting, as well as the narrow analysis window. Vaccinees who continue to be at risk of exposure to Ebola virus should take all available precautions to prevent transmission of Ebola virus from infected individuals. • The duration of protection beyond 31 days after vaccination is unknown. • The effectiveness of V920 for some subpopulations is not established. V920 is being evaluated in children, HIV-infected subjects, and in a large expanded access ring vaccination study in the Democratic Republic of Congo. • The effectiveness for the US population has not been established; however similar immunogenicity was observed between North American and

		Spanish subjects compared to subjects in Sierra Leone and Liberia.
Risk	• Local injection site reactions and systemic symptoms including fever, headache, myalgia, and fatigue were commonly reported, including infrequent severe manifestations of these symptoms. • Events of arthralgia and arthritis were reported more commonly after V920 than placebo in multiple studies, including severe and prolonged reports of arthritis in a single study. Vaccine virus RNA was detected in synovial fluid in some cases. • Events of vesicular rash have been reported more commonly after V920 than placebo in multiple studies. Vaccine virus RNA has been detected in skin biopsies and vesicular fluid in some cases. • Vaccine virus RNA was detected in saliva and serum. The risk of transmission of the vaccine virus to unvaccinated individuals through contact with bodily fluid or contact with vesicular fluid is a theoretical possibility. • Data regarding the safety and reactogenicity of the vaccine when co-administered with other vaccines were not included in the licensure application. • Data regarding the safety and reactogenicity of the vaccine when administered to pregnant and immunocompromised individuals were limited and inconclusive. • Neurovascular events, including cerebrovascular accident, were reported after V920 and were not reported after placebo, although the relationship of these events to V920 has not been established. • Related events of anaphylaxis were reported in two subjects in the clinical development program. • Although the database was adequate for the assessment of safety, an integrated analysis was limited to serious adverse events in blinded studies. Many factors precluded a more extensive pooling of safety data. Studies in the clinical development program were conducted by multiple sponsors using different study designs in different geographical regions. The largest studies were open-label. A larger safety database may elucidate the risks, if any, for imbalances observed, and imbalances of rare events or events for which the effect size may be small.	• Despite limitations in analysis of safety data, the available overall safety profile supports licensure of V920 in adults.
Risk Management	• The proposed risk management plan includes routine risk minimization measures via product labeling and routine surveillance.	• Specific information requested during routine surveillance for exposure during pregnancy. • Labelling includes information on the rate and risk of anaphylaxis.

11.2 Risk-Benefit Summary and Assessment

Data submitted to the BLA establishes a substantial likelihood of benefit of vaccination with V920 in individuals ≥ 18 years of age at risk of exposure to *Zaire ebolavirus.* Risks of V920 include transmission of vaccine virus to unvaccinated contacts, local and systemic reactogenicity, including infrequent severe events, and events of arthritis. Comparison of safety data across studies was limited by variability in the collection and reporting of safety data and limited numbers of subjects in the blinded study populations. In the context of the high morbidity and mortality associated with EVD, the benefit-risk profile of V920 supports approval for the prevention of disease caused by Zaire ebolavirus in individuals 18 years of age and older.

11.3 Discussion of Regulatory Options

The Applicant has requested and the data support traditional approval of V920 for the prevention of disease caused by Zaire ebolavirus in individuals 18 years of age and older.

11.4 Recommendations on Regulatory Actions

The clinical reviewer recommends approval of V920 for the prevention of disease caused by *Zaire ebolavirus* in individuals 18 years of age and older. Please see Sections 11.1 and 11.2 for the rationale for this recommendation.

11.5 Labeling Review and Recommendations

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

Two statements were added to the Limitations of Use section to indicate that the duration of protection conferred by ERVEBO is unknown, and that ERVEBO does not protect against other species of *Ebolavirus* or *Marburgvirus.* The Warnings and Precautions section was revised to include the following: (1) a statement to advise ERVEBO participants to continue to adhere to infection control practices to prevent EVD infection and transmission; (2) a statement that indicates that anaphylaxis has been observed following administration of ERVEBO, and that appropriate medical treatment and supervision must be available in case of anaphylactic event following the administration of ERVEBO; (3) a statement that indicates that vaccine virus RNA has been detected in plasma, saliva, and urine and fluid from skin vesicles after vaccination, and that transmission of vaccine virus is a theoretical possibility.

11.6 Recommendations on Postmarketing Actions

Merck has committed to conduct the following postmarketing activities:

PEDIATRIC REQUIREMENT

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

Final Protocol Submission: October 21, 2016

Study Completion Date: January 31, 2020

Final Report Submission: June 30, 2021

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

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

APPENDIX 1: SUMMARIES OF PHASE 1 BLINDED STUDIES

V920-001: A Phase 1 Randomized, Single-Center, Double-Blind, Placebo-Controlled, Dose-Escalation Study to Evaluate the Safety and Immunogenicity of the BPSC-1001 (VSVΔG-ZEBOV) Ebola Virus Vaccine Candidate in Healthy Adult Subjects

First subject visit: October 13, 2014
Last subject visit: August 25, 2015
Sponsor: BioProtection Systems Corporation (NewLink Genetics Corporation)

V920-001 was a Phase 1 randomized, single-center, double-blind, placebo-controlled, dose-escalation study to evaluate the safety and immunogenicity of the BPSC-1001 (VSVΔG-ZEBOV) Ebola Virus vaccine candidate in healthy adult subjects with a primary objective of assessing safety and tolerability of V920 administered via intramuscular (IM) injection. Secondary objectives included evaluations of ZEBOV-specific antibody responses induced by V920 (binding and neutralizing antibodies) and vaccine viremia and shedding. A total of 39 subjects were planned and enrolled into one of three dosing cohorts of 13 subjects each to receive the following treatments: 3×10^6 pfu/mL V920 or placebo (n= 10 and 3, respectively), 2×10^7 pfu/mL V920 or placebo (n= 10 and 3, respectively), or 1×10^8 pfu/mL V920 or placebo (n= 10 and 3, respectively). A total of two subjects discontinued from the study due to change in residence; however, all 39 subjects met criteria for inclusion in the immunogenicity analysis population (per protocol) and the safety analysis population (all subjects as treated).

No serious AEs or deaths were reported. Solicited adverse events were collected for 14 days after vaccination. Mild to moderate solicited local AEs of pain were observed in 80 to 100% of the subjects in each V920 cohorts compared to 33% of placebo recipients. Systemic solicited AEs with onset <1 day following vaccination were more commonly reported by V920 recipients (80%) compared to placebo recipients (33.3%), while the frequency of solicited systemic AEs with onset 2 to 14 days following vaccination were generally comparable between V920 and placebo recipients. Solicited systemic AEs reported by ≥20% subjects and more frequently by V920 recipients compared to placebo recipients included fatigue, myalgia, chills, subjective and objective fever, nausea, and abdominal pain. Grade 3 solicited systemic AEs were reported by eight V920 recipients and included arthralgia, chills, fatigue, headache, myalgia, subjective and objective fever, and sweats. All Grade 3 events occurred in the first day following vaccination and resolved within a few days and were considered related to study drug. The longest median duration for a solicited systemic AE in the V920 cohorts was for arthralgia (3 days; range: 1 to 6 days) and headache (3 days; range 1 to 8 days).

Hematologic abnormalities, including unsolicited AEs and safety laboratories, were reported more frequently after V920 compared to placebo included decreases in lymphocyte count, white blood cell count, neutrophil count, and platelets, including Grade 3 events of decreased lymphocyte count/lymphopenia reported by 30% of V920 recipients. Generally, decreases in lymphocyte counts had an early onset (Days 1 to 3) and subsided by Day 7 in most subjects.

Detectable viremia was present in 100%, 96.7%, and 20% of V920 recipients on Days 1, 3, and 7, respectively. By Day 14, viremia had resolved in all subjects. Detectable V920

was present in either saliva or urine at any time post-vaccination in 13% of V920 recipients.

Dose-dependent increases in anti-EBOV IgG geometric mean titers, as measured by ELISA, peaked at Day 56 after V920 vaccination and decreased slightly thereafter. Anti-EBOV IgG seroconversion rates (defined as post-vaccination titer ≥ 200 that was also at least a 4-fold increase over baseline) were 96.6% for all time points after Day 14. After every time point after Day 14, the seroconversion rate was 100% in the lower dose cohorts and 90% in the 1 x 10^8 pfu cohort. Neutralizing antibody geometric mean titers, as measured by $PsVNA_{50}$, peaked at Day 28 and decreased thereafter and did not appear to be dose-dependent. By Day 28, 90-100% of subjects had seroconverted (defined as least a 4-fold increase over baseline) based on $PsVNA_{50}$ titers. By Day 180, only 33.3-44.4% of subjects in the lower dose cohorts continued to meet seroconversion criteria, compared to 70% of the subjects at the 1×10^8 pfu V920 dose level.

In summary, solicited reactogenicity events were common after V920 and some were severe. The most common unsolicited events were laboratory abnormalities, most of which were hematologic. Decreases in white blood cells were observed. Increases in GMT and GMFI for $PsVNA_{50}$ and anti-EBOV IgG titers were noted post-vaccination.

V920-002: A Phase 1 Randomized, Double-Blind, Placebo Controlled, Dose-Escalation Study to Evaluate the Safety and Immunogenicity of Prime-Boost VSV Ebola Vaccine in Healthy Adults

First subject visit: October 7, 2014
Last subject visit: December 10, 2015
Sponsor: BioProtection Systems Corporation (NewLink Genetics Corporation)

V920-002 was a Phase 1 randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety and immunogenicity of a 2-dose regimen of BPSC-1001 (VSVΔG-ZEBOV) Ebola Virus vaccine candidate in healthy adult subjects with a primary objective of establishing the maximum safe and tolerated dose level of a two immunization prime-boost regimen using the V920 Zaire Ebola vaccine candidate administered via IM injection. Secondary objectives included evaluations of ZEBOV-specific antibody responses induced by a single and a subsequent dose of V920 (binding and neutralizing antibodies) and vaccine viremia and shedding. A total of 39 subjects were planned and enrolled into one of three dosing cohorts of 13 subjects each to receive the following treatments: 3 x 10^6 pfu/mL V920 or placebo (n= 10 and 3, respectively), 2 x 10^7 pfu/mL V920 or placebo (n= 10 and 3, respectively), or 1 x 10^8 pfu/mL V920 or placebo (n= 10 and 3, respectively). A total of two subjects in the 2 x 10^7 pfu/mL dose group discontinued from the study as they were lost to follow-up; however, all 39 subjects met criteria for inclusion in the immunogenicity analysis population (per protocol) and the safety analysis population (all subjects as treated).

No serious AEs or deaths were reported. Solicited adverse events were collected for 14 days after vaccination. Mild to moderate solicited local AEs of injection site pain were reported by 83% and 63% of the subjects in the combined V920 dose groups after the first and second vaccinations, respectively, compared to 11% of placebo recipients after each vaccination. Systemic solicited AEs were reported by 93% and 50% of the subjects in the combined V920 dose groups after the first and second vaccinations, respectively, compared to 33 and 11% of placebo recipients after the first and second vaccinations, respectively. After the first vaccination, the most frequently reported solicited systemic

AEs in V920 recipients compared to placebo recipients included myalgia (77% and 22%), fatigue (77% and 22%), subjective fever (63% and 11%), headache (60% and 11%), chills (53% and 0%), arthralgia (43% and 0%), objective fever (30% and 0%), and sweats (27% and 0%). After the second vaccination the most frequently reported solicited systemic AEs in V920 recipients compared to placebo recipients included headache (27% and 11%), myalgia (17% and 11%), arthralgia (17% and 0%), fatigue (13% and 11%), subjective fever (13% and 0%), diarrhea (7% and 0%), and objective fever (7% and 0%). Grade 3 solicited TEAEs following the first vaccination were reported in two (7%) of the 30 subjects who received V920 and included reports of fatigue (7%) and headache, objective fever, subjective fever, and hyperhidrosis (3% each). One subject reported a Grade 3 event of subjective fever following the second vaccination. The frequency of events was generally comparable across the dosing groups. Solicited events were frequently reported in all V920 dosing groups but were generally mild to moderate in severity and short in duration. No clear pattern of dose-dependence in the frequency and severity of solicited AEs was noted.

After the first vaccination, unsolicited AEs reported by more than one subject and reported more frequently after V920 than placebo included lymphocyte count decreased (13% and 11%), neutrophil count decreased (20% and 0%), white blood cell count decreased (13% and 0%), abdominal pain, oral disorder, chest discomfort, upper respiratory tract infection, alanine aminotransferase increased, aspartate aminotransferase increased, hemoglobin decreased, and hematuria (7% and 0% each). After the second vaccination, unsolicited AEs reported by more than one subject and reported more frequently after V920 than placebo included neutrophil count decreased (13% and 11%), alanine aminotransferase increased (10% and 0%), white blood cell count decreased (10% and 0%), lymphadenopathy (7% and 0%), and hematocrit decreased (7% and 0%). One subject in the 1×10^8 pfu V920 dose group reported an unrelated Grade 3 event of hematuria on Day 1 following the first vaccination. Following the second vaccination, unrelated events of ≥ Grade 3 severity were reported by three (10%) subjects who received V920, including hyperglycemia (one subject, 3%), glycosuria (one subject, 3%), increased blood creatine phosphokinase (one subject, 3%), and hematuria (two subjects, 10%). There was no pattern of events to suggest a dose-dependent relationship between specific unsolicited events and V920.

In the first 14 days after the first vaccination, 50% of subjects in the 3×10^6 pfu dose group reported arthralgia, compared to 40% of subjects in each of the higher dose groups. In the first 14 days after the second vaccination, solicited events of arthralgia were reported in 10% of subjects in the 3×10^6 and 1×10^8 pfu dose groups and 30% of subjects in the 2×10^7 pfu dose group. Notably, two subjects reported arthralgia after each vaccination. No subject in the placebo group reported arthralgia after either vaccination. Most events were considered related to vaccine and all events were Grade 1 to 2 in severity. The median duration of solicited events of arthralgia across subjects who received V920 was 3 days (range: 1 to 10 days). Treatment for arthralgia was required for 20% of subjects and included ibuprofen, naproxen, and paracetamol. No unsolicited events of arthralgia were reported within 14 to 28 days of the first or second vaccination. One subject reported arthralgia on Day 70, which was assessed as Grade 1 in severity and possibly related to vaccination. The subject did not receive any medication to treat this event and it was ongoing at the end of study. No events of arthritis were reported in this study.

Hematologic abnormalities, including unsolicited AEs and safety laboratories, were reported more frequently after V920 compared to placebo and included decreases in lymphocyte count, white blood cell count, and neutrophil count, and platelets. Adverse events associated with hematologic abnormalities considered related to study product were reported with similar frequency in V920 recipients (27%) and placebo recipients (22%). ALT elevations were observed after V920 in 4% to 10% of subjects at each time point. All events were Grade 1 with the exception of a Grade 2 elevation in ALT observed at the Day 35 visit. ALT elevations were not observed in placebo recipients. AST elevations were observed after V920 in 3 to 7% of subjects at each time point. Grade 2 elevations in AST were observed in one subject each at the Day 7, 28, and 35 visits; all other AST elevations were Grade 1 in severity. No bilirubin abnormalities were associated with transaminase elevations.

Detectable viremia was present in 100% of V920 recipients on Day 3. By Day 7, viremia was not present in any subjects who received 3 x 10^6 pfu of V920 and was present in 30% of subjects in both the higher dose V920 groups. No viremia was detected after the second vaccination except for one subject in the 1×10^8 pfu V920 group on Day 31 (3 days after the second vaccination). On Day 35, 7 days after the second vaccination, none of the subjects had detectable viremia. Detectable V920 was present in saliva at any time post-vaccination in 24% of V920 recipients. V920 was present in the saliva of 2 subjects (20%) in the 3×10^6 pfu dose group on Day 3 and was present in four subjects (40%) in the 2×10^7 pfu dose group and one (11%) subject in the 1×10^8 pfu dose group on Day 7. No V920 RNA was detected in urine. None of the subjects had detectable V920 RNA in urine or saliva following the second vaccination on Day 31 and Day 35.

At all time points through Day 180, the anti-EBOV IgG titers were significantly dose-dependent. In all cohorts, the GMT and GMFI peaked at Day 42 and decreased slightly thereafter. By Day 360, the GMT had decreased in all groups but remained higher than baseline. A second dose of vaccine had a limited impact on GMTs. By Day 14, 30%, 100%, and 78% of subjects in the 3×10^6 pfu, 2×10^7 pfu, and 1×10^8 pfu V920 dose groups, respectively, met seroconversion criteria (i.e., a post-vaccination titer ≥200 that was also at least a 4-fold increase in ZEBOV IgG ELISA titer compared to baseline). By Day 28, all but a single subject in the lowest V920 dose groups had seroconverted; this subject seroconverted 2 weeks after the second vaccination. For all time points subsequent to Day 28, all subjects were seroconverted.

$PsVNA_{50}$ titers were detectable in all dosing groups by Day 28, peaked at Day 56, and were significantly higher in the higher dosing groups. A second dose of vaccine resulted in a limited increase in GMT. $PsVNA_{50}$ titers and seroconversion rates (at least a 4-fold increase over baseline) decreased over time.

In summary, solicited reactogenicity events were common after V920 but did not appear to be dose-related. The most common unsolicited events were laboratory abnormalities, most of which were hematologic. Decreases in white blood cells were frequently seen; all events were Grade 1 to 2, none were associated with infectious events, and there did not appear to be an association with the dose level. Dose-dependent increases in GMT and GMFI for $PsVNA_{50}$ and anti-EBOV IgG titers were noted after the first vaccination. A second vaccination with V920 resulted in a limited increase in titers.

V920-003: A Phase 1 Randomized, Single-Center, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Immunogenicity of the

BPSC-1001 (VSVΔGZEBOV) Ebola Virus Vaccine Candidate in Healthy Adult Subjects

First subject visit: November 18, 2014
Last subject visit: June 12, 2015
Sponsor: Dalhousie University/ Izaak Walton Killam (IWK) Health Centre and BioProtection Systems Corporation (NewLink Genetics Corporation)

V920-003 was a single-center, randomized, double-blind, placebo-controlled dose-ranging study of V920 delivered by IM injection in healthy adult subjects with a primary objective of assessing safety and tolerability and secondary objectives including evaluation of the ZEBOV-specific antibody responses and vaccine viremia and excretion. A total of 40 subjects were randomly assigned in a ratio of 1:1:1:1 to one of the 3 V920 dose groups (1×10^5, 5×10^5, or 3×10^6 pfu/mL) or the placebo (normal saline) control group. All 40 subjects were vaccinated, completed the study, and met criteria for inclusion in the immunogenicity analysis population (per protocol) and the safety analysis population (all subjects as treated).

One serious adverse event of unrelated Grade 4 cholelithiasis was reported 159 days after vaccination with V920. No deaths or withdrawals due to AEs were reported.

Injection site pain was the only solicited local AE reported. Grade 1 to 2 injection site pain was reported by 53% of subjects who received V920 (20%, 50%, and 90% of subjects in the 1×10^5, 5×10^5, and 3×10^6 pfu cohorts, respectively) and 30% of subjects who received placebo. The majority of events had a time to onset of ≤1 day following vaccination, with a maximum duration of 5 days and a median duration of 2 days for the combined V920 cohorts. Solicited systemic AEs were reported by 80% of subjects who received V920 and 100% of subjects who received placebo. Solicited systemic AEs were more frequently reported after higher doses of V920 (80% and 90% of subjects in the 5×10^5 and 3×10^6 pfu cohorts, respectively) compared to the lowest dose cohort (70% of subjects in the 1×10^5 pfu group). The majority of solicited systemic AEs had a time to onset within 7 days following vaccination. Most solicited systemic AEs were Grade 1 to 2; a total of three subjects reported Grade 3 events. Solicited systemic AEs that were reported by more than one subject and more common in V920 recipients compared to placebo recipients included arthralgia (40% and 20%), chills (23% and 20%), abdominal pain (17% and 10%), and sweats (13% and 10%). All events of arthralgia reported within 14 days post-vaccination were assessed as Grade 1 or Grade 2 in severity and were considered by the investigator as probably or possibly related to V920. The median duration of solicited events of arthralgia was 3.5 days (range: 1 to 9 days) for V920 recipients and 3.5 days (range: 3 to 4 days) in the 2 subjects in the placebo cohort. The majority of solicited AEs of arthralgia resolved without treatment; oral anti-inflammatory preparations were administered to one subject in the 3×10^6 pfu cohort and one subject in the placebo cohort.

The majority of unsolicited AEs were reported as Grade 1 or Grade 2; an unrelated Grade 3 AE of sinus pain, an unrelated Grade 4, non-serious AE of increased ALT, and a related Grade 3 event of wrist arthralgia were reported by subjects in the 5×10^5 pfu V920 dose cohort. Unsolicited AEs reported by more than one subject and reported more frequently after V920 than placebo included pyrexia (7% and 0%); nasopharyngitis (13% and 10%); alanine aminotransferase increased and arthralgia (10% and 0% each); aspartate aminotransferase increased, neutrophil count decreased, and prothrombin time prolonged (7% and 0% each). Unsolicited AEs related to vaccination were reported

by 33% of subjects in the combined V920 group and 10% of subjects in the placebo group. The majority of the vaccine-related AEs following first vaccination were laboratory abnormalities. Unsolicited related AEs reported by more than one subject after V920 included pyrexia (7% of subjects), ALT increased (7% of subjects), prothrombin time prolonged (7% of subjects), and arthralgia (7% of subjects). Unsolicited events of arthralgia were reported by three subjects within 14 to 28 days of vaccination, including a Grade 1 related event of intermittent arthralgia (joint pain in hands) from Days 15 to 137 in a 45-year-old female (1×10^5 pfu cohort), a Grade 1 related event of arthralgia of the right wrist and Grade 3 related event of arthralgia of the left wrist in a 38-year-old male on Days 18 and 19 (5×10^5 pfu cohort), and a Grade 1 unrelated event of bilateral arthralgia in the hips in a 22-year-old female on Days 26 and 27 (3×10^6 pfu cohort). A 49-year-old female in the 3×10^6 pfu V920 dose cohort reported joint swelling in the left knee from Day 13 to Day 26, treated with anti-inflammatory medication.

ALT elevations were observed after V920 in 4% to 15% of subjects in V920 combined cohorts and in 10% to 20% of subjects in the placebo cohort at each time point. All ALT elevations were Grade 1 with the exception of a Grade 4 elevation observed at the Day 28 visit and a Grade 3 elevation observed at the Day 180 visit, both of which occurred in subjects in the 5×10^5 pfu cohort. AST elevations were observed in 0% to 15% of subjects in the combined V920 cohorts and 0% to 10% of subjects in the placebo cohort at each time point, all of which were Grade 1 to 2.

Overall, 63% of subjects in the V920 dosing groups had vaccine viremia at any time post-vaccination, including 50% of subjects in each of the lower dosing groups and 90% of subjects in the 3×10^6 pfu group. The peak of viremia in copies per mL and number of subjects was observed at Day 3 (50% of subjects in each of the lower dosing groups and 80% of subjects in the 3×10^6 pfu group). The geometric mean of the copy number of V920 was 1406 in the 3×10^6 pfu group and between 522 and 561 in the lower dose cohorts. None of the subjects in the study had detectable V920 in urine or saliva at any time point.

In the 3×10^6 pfu cohort, the ZEBOV IgG ELISA GMTs and GMFI peaked at Day 28 (1321 ELISA Units and 48, respectively) and decreased slightly thereafter through Day 180. In the lower dose cohorts, the GMTs and GMFIs continued to increase slightly through Day 180. In a pairwise comparison, there was no statistically significant difference in the Day 28 GMTs between the V920 dosing cohorts. Only one subject (1×10^5 pfu dosing cohort) did not meet the criteria for seroconversion at any time post-vaccination following vaccination with V920. $PsVNA_{50}$ titers were detectable in all dosing groups by Day 28, peaked at Day 56, and were comparable across dosing groups.

In summary, solicited reactogenicity events were common after V920, some of which were more frequently observed in the highest dosing cohort. Events of arthralgia and arthritis were reported following V290. Decreases in leukocyte and neutrophil count at Day 3 after V920 were observed both at the individual subject level and at the combined group level. Increases in GMT and GMFI for $PsVNA_{50}$ and anti-EBOV IgG titers were noted after V920 and did not appear to be dose-dependent.

V920-004: A Phase 1 Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Dose-Response Study to Evaluate the Safety and Immunogenicity of the BPSC1001 (VSVΔG-ZEBOV) Ebola Virus Vaccine Candidate in Healthy Adult Subjects

First subject visit: December 8, 2014
Last subject visit: June 23, 2016
Sponsor: BioProtection Systems Corporation (NewLink Genetics Corporation)

V920-004 was a multi-center, randomized, double-blind, placebo-controlled, dose-ranging study of the V920 delivered by IM injection. Subjects were enrolled in two sequential cohorts; Cohort 1 was designed to define a potential dose-sparing regimen, and Cohort 2 was designed to bracket the selected adult dose of 2×10^7 pfu evaluated during the conduct of the Phase 3 trials in West Africa.

In Cohort 1, 330 healthy adults 18 to 60 years of age were randomized in a 64:64:64:64:74 ratio to receive 3×10^3, 3×10^4, 3×10^5, or 3×10^6 pfu V920, or placebo (normal saline). Sentinel cohorts of 10 subjects in each treatment group and 20 subjects in the placebo group were followed for 14 days prior to enrollment of the remaining subjects in each group. In Cohort 2, 182 healthy adults 18 to 60 years of age were planned to be randomized in a 16:50:50:50:16 ratio to receive 3×10^6, 9×10^6, 2×10^7, or 1×10^8 pfu V920, or placebo. Cohort 2 included a common dose level with Cohort 1 (3×10^6 pfu) to bridge to the same dose group in Cohort 1.

Immunogenicity assessments were collected on Days 0, 7, 14, 28, 56, 84, 180, and 360. In Cohort 1, all V920 recipients had samples evaluated for immunogenicity and 25 placebo recipients were randomly selected for immunogenicity evaluations. All subjects in Cohort 2 were included in immunogenicity analyses. Solicited AEs included redness, swelling, or pain at the site of the injection, subjective and objective fever, chills, sweats, myalgia, arthralgia, fatigue, headache, skin or mucosal lesions, arthritis, and gastrointestinal symptoms (nausea, vomiting, abdominal pain, and/or diarrhea) and were collected for 14 days after vaccination using scripted questions. Subjects recorded an oral temperature for 14 days after each vaccination. Unsolicited AEs were collected for 28 days after vaccination and SAEs were collected until the end of the study. In Cohort 2 only, additional data was collected for joint symptoms, mouth ulcers, mucosal lesions, and rash between Days 15 and 56 using memory aids and scripted questions. Subjects in Cohort 2 with suspected or confirmed diagnosis of post-vaccination arthritis (Day 5 onwards) or petechial, purpuric, or vesicular rash were promptly evaluated according to standardized algorithms by investigators skilled in rheumatologic and dermatologic assessments, including laboratories.

Of 512 vaccinated subjects, a total of 488 (95%) completed the study through Day 360 with 24 premature withdrawals (V920, 23 subjects; placebo, one subject). The reasons for premature withdrawal included lost to follow-up (n = 15), withdrawal of consent (n = 3), investigator decision (n = 1), and other reasons, such as relocation or incarceration (n = 4). There was one death in the 3×10^6 pfu V920 dose group that was considered unrelated to V920 (head trauma).

Three subjects reported additional unrelated serious adverse events including Grade 4 chest pain, Grade 1 presyncope, Grade 3 peripheral ischemia, and Grade 3 ulna fracture.

Across all V920 dose groups, 43.1% of subjects reported any solicited local event, including events of arm pain (29.7% of subjects), local tenderness (35.4% of subjects), redness (1.9% of subjects), and swelling (1.4% of subjects). In the placebo group, 10.6% of subjects reported any local event, including events of arm pain (7.4% of subjects) and local tenderness (8.5% of subjects). Although each solicited local event

was reported by a higher proportion of subjects in the highest dose groups (9 x10^6 through 1 x 10^8 pfu groups) compared to lower dose groups, the proportions of subjects reporting each event was comparable between the high dose groups. The proportion of subjects reporting arm pain and local tenderness was between 50.0% and 59.6% across all these highest dose groups. With the exception of a single subject in Cohort 1, all events of redness and swelling occurred in the highest dose groups. In each dosing group, the median time to onset of local events was between 0 and 1.5 days, and all events had an onset within 8 days of vaccination. The median duration of local symptoms was generally 3 days or fewer in most dosing groups; a single outlier in the 3 x 10^6 pfu group of Cohort 1 had ongoing arm pain and tenderness through the final study visit. Most events were Grade 1 and none were Grade 3. Local events of moderate severity were more frequently reported in the 1 x 10^8 pfu group than all other dose groups.

Across all V920 dose groups, 59.6% of subjects reported any solicited systemic event, compared to 41.5% of subjects in the placebo group. The proportions of subjects reporting solicited systemic AEs was dose dependent; solicited systemic events were more frequently reported after higher doses of V920 (74.5% and 75.0% of subjects in the 2 x 10^7 and 1 x 10^8 pfu cohorts, respectively) compared to the lower dose cohorts (40.6% to 59.4% of subjects in the 3 x 10^3 through 3 x 10^5 pfu groups). Almost all solicited systemic adverse events were reported by a higher proportion of subjects in the 2 x 10^7 and 1 x 10^8 dose groups compared to the placebo group. In these dose groups, the most frequently reported solicited systemic adverse events included headache (43.8 to 46.8% of subjects after V920 and 27.7% of subjects after placebo); fatigue (38.3% to 45.8% of subjects after V920 and 19.1% of subjects after placebo); myalgia (33.3% to 34.0% of subjects after V920 and 10.6% of subjects after placebo); shivering/chills (27.7% to 31.3% of subjects after V920 and 7.4% of subjects after placebo); subjective fever (29.2% to 29.8% of subjects after V920 and 2.1% of subjects after placebo); and sweats (23.4% to 27.1% of subjects after V920 and 3.2% of subjects after placebo). The majority of solicited systemic AEs had a time to onset within 7 days following vaccination. The median duration of systemic events (excluding joint and skin related events) was between 1 and 3 days. Most solicited systemic AEs were Grade 1 to 2; a total of 8 subjects reported Grade 3 events.

At least one unsolicited AE was reported within 28 days of vaccination by 34.9% of subjects who received V920 and 43.6% of subjects who received placebo. The majority of unsolicited AEs were reported as Grade 1 or Grade 2. A total of 11 Grade 3 unsolicited AEs were reported, including anemia (3×10^5 pfu group), blood glucose decreased (2×10^7 pfu group), cellulitis (3×10^5 pfu group), chills (3×10^6 pfu group), dizziness (3×10^6 pfu group), hemorrhoids (3×10^5 pfu group), hypoglycemia (1×10^8 pfu group), hyperhidrosis (3×10^6 pfu group), pain in extremity (3×10^5 pfu group), pyrexia (3×10^6 pfu group), and sciatica (3×10^5 pfu group). Unsolicited AEs related to vaccination with onset within 28 days following the first vaccination were reported by 14% of subjects who received V920 and 8.5% of subjects who received placebo. Unsolicited related AEs reported by more than 2 subjects after V920 and reported more frequently after V920 than placebo included lymphadenopathy, injection site reactions (bruising, laceration, pruritis), pyrexia, oral herpes, arthralgia, back pain, musculoskeletal stiffness, dizziness, paresthesia, headache, ecchymosis, and rash.

Overall, 4.5% (19 subjects) of V920 recipients met the definition of temporally-associated arthritis compared to 3.2% of placebo recipients (three subjects). In Cohort

1, between 4.7% to 6.3% of subjects in each dose group reported arthritis, compared to 1.4% of subjects in the placebo group. The median time to onset was between 8 and 14 days after V920 and 6 days after placebo. The median duration was between 8 to 19 days after V920 and 47 days after placebo. In Cohort 2, between 2.1% to 5.0% of subjects in each dose group reported arthritis, compared to 10% of subjects in the placebo group. The median time to onset was between 12 and 17 days after V920 and 17.5 days after placebo. The median duration was between 3 to 7 days after V920 and 118 days after placebo. All cases of post-vaccination arthritis resolved in subjects vaccinated with V920, although one subject in the 3×10^6 pfu dose group reported a recurrence of arthritis 2 days after the end date of her initial episode of post-vaccination arthritis.

In Cohort 1, between 3.1% to 6.3% of subjects in each dose group reported dermatitis events, compared to 2.7% of subjects in the placebo group. The median time to onset was between 8.5 and 12.5 days after V920 and 29 days after placebo. The median duration was between 5 to 8.5 days after V920 and 236.5 days after placebo. In Cohort 2, between 5.0% to 8.5% of subjects in each dose group reported dermatitis, compared to 5.0% of subjects in the placebo group. The median time to onset was between 2 and 19 days after V920 and 3 days after placebo. The median duration was between 3 to 8 days after V920 and 5 days after placebo. All cases of post-vaccination dermatitis resolved in subjects vaccinated with V920.

Viremia was detected in 19.6% of V920 recipients at one or more time points post-vaccination. At the lower dose range (3×10^3 through 3×10^5 pfu), only one subject in each group (1.6%) was viremic at any time post-vaccination; however, the duration of viremia was between 5 and 14 days. In the intermediate dose range (3×10^6 through 2×10^7 pfu), 10% to 38.1% of subjects were viremic at any time post-vaccination, with the highest proportion of viremic subjects in the 1×10^8 pfu dose group (62.2%). The highest prevalence of viremia was observed on Days 1 and 2 (12.7% to 12.9% of V920 recipients) compared to all other time points (0-2.2% of V920 recipients). The median duration of viremia was 2 days for these dose groups except the 2×10^7 pfu group, wherein the median duration was 3 days. By Day 28, no subjects were viremic. Viral shedding/excretion in viremic subjects who were at or above the LLOQ of V920 in plasma were tested for the presence of V920 in saliva and urine on Days 1, 2, 3, 4, 7, 14, and 28 post-vaccination. Vaccine shedding in saliva or urine was observed in only 1 subject who received 3×10^3 pfu V920. Vaccine virus was first detectable in saliva at Day 3 and in urine at Day 7, both of which were no longer detectable by Day 14.

Dose-dependent humoral immunogenicity of the vaccine was demonstrated by ZEBOV-GP ELISA as well as $PRNT_{60}$ assay, with peak levels generally observed at Day 56 with plateau or slight decline noted through the Day 360 time point. Parametric and nonparametric pairwise comparisons indicated that all ZEBOV-GP ELISA GMTs for V920 dose groups were significantly higher versus placebo at Day 28 ($p < 0.001$) The ELISA GMTs for the 2×10^7 pfu and 1×10^8 pfu V920 dose groups were significantly higher than the GMTs for the 3×10^3, 3×10^4, 3×10^5, and 9×10^6 pfu V920 dose groups. The 1×10^8 pfu V920 dose group also had significantly higher GMTs versus the combined 3×10^6 pfu and for the Cohort 1, but not the Cohort 2, 3×10^6 pfu V920 dose group ($p < 0.05$ for parametric and nonparametric comparisons). The $PRNT_{60}$ GMTs appear to be dose-dependent, with the highest GMTs observed in the 2×10^7 and 1×10^8 pfu dose groups. The $PRNT_{60}$ GMTs for the 1×10^8 pfu group were significantly higher ($p < 0.05$ for

parametric and nonparametric comparisons) than all other dose groups except the 2×10^7 pfu dose group.

In summary, immunogenicity data from this study supported the selection of the 2 x 10^7 pfu dose for further clinical development. The proportions of subjects reporting joint-related events was lower in this study than was observed in V920-005. The reactogenicity profile of V920 observed in this study was consistent with other Phase 1 studies. No new safety signals were identified.

V920-005: A Phase I/II Dose-Finding Randomized, Single-Center, Double-Blind, Placebo-Controlled Safety and Immunogenicity Trial of the Vesicular Stomatitis Virus-Vectored Zaire Ebola Candidate Vaccine BPSC1001 (VSVΔG-ZEBOV) In Healthy Adults

First subject visit: November 10, 2014
Last subject visit: January 16, 2016
Sponsor: University Hospitals of Geneva

V920-005 was a single-center, randomized, double-blind, placebo-controlled dose-finding study of V920 delivered by IM injection in healthy adult subjects 18 to 65 years of age. The primary objectives included assessing safety and tolerability and determining differences in immunogenicity at Day 28 by dose level using ZEBOV-GP IgG ELISA (in EU/mL and endpoint titers) and $PsVNA_{50}$ and $PsVNA_{80}$. Secondary objectives including evaluation of the ZEBOV-specific antibody responses at other time points, seroconversion rates, and vaccine viremia and excretion. Initially, 115 subjects were planned to be enrolled and receive a single injection of 1×10^7 pfu V920, 5×10^7 pfu V920, or placebo (normal saline). Enrolled subjects consisted of either frontline workers (FLW) who had potential to be deployed to areas affected by the Ebola epidemic or non-deployable adults. The first four deployable FLW subjects were to be administered an open-label 1×10^7 dose of V920. However, this sentinel open-label group was expanded in a protocol amendment to include an additional 15 subjects (7 FLW and 8 non-deployable) to provide additional safety data. Thereafter, FLW were randomized in a 1:1 ratio to receive 1×10^7 or 5×10^7 pfu of V920; non-deployable subjects were randomized 1:1:1 to receive 1×10^7 or 5×10^7 pfu of V920 or placebo. Immunogenicity assessments were collected on Days 7, 14, 28, 84, 168, and 365. Following vaccination, solicited local and systemic events were collected for 14 days, unsolicited events were collected for 28 days, and SAEs were collected for the duration of study participation (through Day 365).

After vaccination of 59 subjects, the Principal Investigator made the decision to hold the study temporarily due to concerns that the vaccine was causing arthritis in four subjects. The Investigators concluded that the findings were dose-related and decided to resume the study using a V920 dose of 3 x 10^5 pfu. After resumption of the study, FLW received a single, open-label dose of 3×10^5 pfu V920 and non-deployable subjects were randomized 7:1 to receive 3×10^5 pfu V920 or placebo.

A total of 115 subjects were randomized into the study, all of whom received the treatment to which they were allocated: 3 x 10^5 pfu V920 (n= 51), 1 x 10^7 pfu V920 (n= 35), 5 x 10^7 pfu V920 (n= 16), or placebo (n= 13). Of the 51 subjects who received the 3 x 10^5 pfu dose, 13 were open-label. Of the 35 subjects who received the 1 x 10^7 pfu dose, 19 were open-label. The remaining doses were administered in a blinded fashion. All 115 subjects were included in safety analyses (all subjects as treated population); 11

subjects were excluded from the per protocol population for immunogenicity analyses due to immunogenicity samples collected outside of the allowed window (n= 10) and a protocol deviation involving receipt of a second dose of V920 outside of the study (n= 1).

Two unrelated serious adverse events due to trauma were reported after V920. No deaths or withdrawals due to adverse events (AEs) were reported.

Across all V920 dose groups, 52.0% of subjects reported any solicited local event, including events of injection site pain (49% of subjects), redness (2.9% of subjects), and swelling (3.9% of subjects). In the placebo group, 23.1% of subjects reported any local event, all of which were events of injection site pain. Injection site pain was reported by a higher proportion of subjects in the 1×10^7 and 5×10^7 pfu groups (75.0% to 77.1%) compared to the 3×10^5 pfu group (21.6%). Most events were Grade 1 and none were Grade 3. In each dosing group, the median time to onset of injection site pain was 0-1.0 days, and all events had an onset within 3 days of vaccination. The median duration of local symptoms was 2 days or fewer across dosing groups. Prolonged events of redness and swelling with a duration of 8 and 6 days, respectively, were reported by one subject each in the 5×10^7 pfu group.

Across all V920 dose groups, 91.2% of subjects reported any solicited systemic event, compared to 69.2% of subjects in the placebo group. The proportions of subjects reporting solicited systemic AEs was comparable across the dosing groups (88.2% to 94.3%), although some solicited systemic events (chills, headache, myalgia, fever) were more frequently reported after higher doses of V920 compared to the 3×10^5 pfu group. Grade 3 solicited systemic events reported after V920 included arthritis (9.8% of subjects), chills (5.9% of subjects), myalgia (5.9% of subjects), fatigue (3.9% of subjects), subjective fever (3.9% of subjects), headache (2.0% of subjects), and nausea (1.0% of subjects). No Grade 3 or higher solicited systemic events were reported in placebo recipients. The median time to onset for chills, fatigue, headache, loss of appetite, myalgia, nausea, and objective and subjective fever was ≤ 1 day after V920. The median duration for the most frequently reported events (≥5% of subjects) was 2 days or fewer. Exceptions included fatigue, with a median duration of 3 days, and arthritis, with a median duration of 34.5 days for the initial report of arthritis (range: 4 to 330 days).

At least 1 unsolicited AE was reported within 28 days of vaccination by 74.5% of subjects who received V920 and 53.8% of subjects who received placebo. The proportions of subjects reporting unsolicited events were comparable across the V920 doe groups (71.4% to 87.5%). The majority of unsolicited AEs were reported as Grade 1 or Grade 2. Grade 3 unsolicited events included eye pain, facial pain, alcoholic hepatitis, arthritis, muscle spasms, and carpal tunnel syndrome in the 3×10^5 pfu group, and rhabdomyolysis and an intervertebral disc protrusion in the 5×10^7 pfu group. Grade 3 unsolicited events considered related included arthritis and carpal tunnel syndrome. No Grade 3 unsolicited events were reported in the placebo group.

Arthritis events were reported by 23.5% of subjects who received V920 (n= 24), half of whom (n= 12) reported severe events. Recurrent arthritis was reported by 4.9% of V920 recipients (n= 5). The proportions of subjects reporting arthritis events were comparable across the dose groups (18.8% to 25.5%). Arthritis events were not reported in the placebo group. The overall median time to onset to arthritis events in V920 recipients was 10.5 days, ranging from 6 to 18 days, with the interquartile range of onset from 9 to

14 days. Median onset times were 10.0, 10.5, and 14 days following vaccination at 3×10^5 pfu, 1×10^7 pfu, and 5×10^7 pfu V920, respectively. The overall median duration of the initial report of arthritis events was 34.5 days, with median durations of 31, 56, and 137 days in the 3×10^5 pfu, 1×10^7 pfu, and 5×10^7 pfu V920 dose groups, respectively. The most commonly involved joints included the fingers, wrist, and knee. Joint (synovial fluid) samples from three subjects were positive for vaccine virus RNA by rVSV PCR on Days 14, 14, and 28, respectively. A total of 11 subjects in V920 dose groups (11%) had coincident symptoms of arthritis and dermatitis, including seven subjects in the 3×10^5 pfu group (13.7%), two subjects in the 1×10^7 pfu group (5.7%), and two subjects in the 5×10^7 pfu group (10.8%).

Overall, 29.4% of subjects in the V920 group reported any skin- or mucosal-related event, compared to 30.8% of placebo recipients. Skin- or mucosal-related events were reported by 31.4%, 22.9%, and 37.5% of subjects in the 3×10^5, 1×10^7, and 5×10^7 dose groups, respectively. All events were mild to moderate in severity. A total of eight skin samples from five subjects were positive for the presence of vaccine virus RNA by RT-PCR. Three subjects in the 3×10^5 pfu group each had a skin sample that was positive for V920 on Day 7, Day 14, and Day 14, respectively. One subject in the 1×10^7 pfu group and had four skin samples that were positive for V920 (two on Day 7 and 2 on Day 14) and one subject in the 5×10^7 pfu group had a skin sample that was positive on Day 28. Immunostaining was performed for 2 subjects with a papular and vesicular lesion, respectively that were biopsied and positive for the presence of V920.

Decreases in neutrophils, lymphocytes, and leukocytes were commonly observed after V920; these decreases were transient and mild to moderate in severity.
Viremia was detected in 52.2% of V920 recipients at any time point post-vaccination. Vaccine viremia was dose dependent; in the 3×10^5 pfu group, viremia was observed in 10.2%, 12.2%, and 2.0% of subjects at Days 1, 3, and 7, respectively, compared to 78.1%, 81.3%, and 3.2% of subjects in the 1×10^7 pfu group, respectively, and 90.9%, 63.5%, and 0% of subjects in the 5×10^7 pfu group, respectively. All subjects in the 5×10^7 pfu group were viremic at any time point after vaccination. At Days 14 and 28, no subjects in any group were viremic, although testing was conducted only in a very limited number of subjects (n= 6 at Day 14 and n= 8 at Day 28). All subject samples were planned to be tested for viral RNA shedding in saliva and urine following vaccination on Days 1, 3, and 7 and a subset of at least the first 10 subjects were to be tested for vaccine leakage at the site of injection as determined by rVSV RT-PCR of skin swabs of the injection site 1 hour post-vaccination. Testing was stopped after the first 10 subjects, as few samples were positive. Of the subjects tested, five on Day 1 and five on Day 3 had detectable but not quantifiable V920 in their urine and saliva. No skin swabs were positive on Day 0.

At Day 28, ZEBOV-GP ELISA GMTs were dose dependent. In the 3×10^5 pfu, 1×10^7 pfu, and 5×10^7 pfu V920 dose groups, GMTs in EU/mL at Day 28 were 257.3, 837.0, and 1465.7, respectively, and GMFIs were 8.6, 25.5, and 44.2, respectively. In the 3×10^5 pfu, 1×10^7 pfu, and 5×10^7 pfu V920 dose groups, GMT endpoint titers at Day 28 were 337.6, 1083.4, and 1814.9, respectively, and GMFIs were 12.9, 32.0, and 53.0, respectively. In both endpoint titers and EU/mL, GMTs at Day 28 were statistically higher for the 1×10^7 pfu and 5×10^7 pfu V920 dose groups compared to the 3×10^5 pfu dose group. For secondary immunogenicity endpoints, data were only available for baseline and Days 28, 84, and 168. Peak GMTs in EU/mL were observed at Day 84, at which time a dose-

dependent relationship was still apparent. By Day 168, GMTs in EU/mL decreased in all dose groups and were generally comparable, while GMT endpoint titers were increased at the Day 168 visit compared to all previous time points for the 3×10^5 pfu and 1×10^7 pfu groups.

For both ELISA GMTs in EU/mL and endpoint titers, seroconversion rates were dose-dependent at each time point, although the dose-dependent difference was most pronounced at Day 28. For ELISA titers (EU/mL), the seroconversion rate was 100% in the 5 x 10^7 pfu group and 93.3% to 100% in the 1 x 10^7 pfu group at all time points. For ELISA endpoint titers, the seroconversion rate was 100% in the 5 x 10^7 pfu group and 96.9% to 100% in the 1 x 10^7 pfu group at all time points.

At Day 28, $PsVNA_{50}$ and $PsVNA_{80}$ GMTs were dose dependent. In the 3×10^5 pfu, 1×10^7 pfu, and 5×10^7 pfu V920 dose groups, $PsVNA_{50}$ GMTs at Day 28 were 337.6, 1083.4, and 1814.9, respectively, and GMFIs were 12.9, 32.0, and 53.0, respectively. The PsVNA50 GMTs for the 1×10^7 and 5×10^7 pfu dose groups were significantly higher than the 3×10^5 pfu dose group and the PsVNA50 GMT for the 5×10^7 pfu dose group was significantly higher ($p = 0.03$ for parametric pairwise comparison) than the 1×10^7 pfu dose group. For secondary immunogenicity endpoints, data were only available for baseline, Day 28, and Day 168. The $PsVNA_{50}$ GMTs decreased at the Day 168 time points, with GMFIs that reflected minor increases over baseline across the dose groups (1.2 to 1.9). In the 3×10^5 pfu, 1×10^7 pfu, and 5×10^7 pfu V920 dose groups, $PsVNA_{80}$ GMTs at Day 28 were 12.4, 19.1, and 29.4, respectively, and GMFIs were 1.2, 1.9, and 2.9, respectively. By Day 168, $PsVNA_{80}$ GMFIs reflected that GMTs were comparable to baseline (1.0 to 1.2).

For $PsVNA_{50}$, the Day 28 seroconversion rate in the 3 x 10^5 pfu group was 38.8% compared to 75.0% and 100% in the 1 x 10^7 and 5 x 10^7 pfu groups, respectively. The Day 168 seroconversion rate in the 3 x 10^5 pfu group was 19.1% compared to 26.7% and 9.1% in the 1 x 10^7 and 5 x 10^7 pfu groups, respectively. Overall, 60.9% of all subjects who received any V920 dose seroconverted at any time post-vaccination. For $PsVNA_{80}$, the Day 28 seroconversion rate in the 3 x 10^5 pfu group was 6.1% compared to 25.0% and 54.5% in the 1 x 10^7 and 5 x 10^7 pfu groups, respectively. The Day 168 seroconversion rate in the 3 x 10^5 pfu group was 4.3% compared to 0% in both the 1 x 10^7 and 5 x 10^7 pfu groups. Overall, 19.6% of all subjects who received any V920 dose seroconverted at any time post-vaccination.

In summary, solicited reactogenicity events were common after V920, some of which were more frequently observed in the highest dosing cohort. Events of arthritis were reported by a high proportion of subjects following V290, including severe and recurrent events, although the events did not appear to be dose-dependent. Vaccine virus RNA was detected in both synovial fluid and skin. Decreases in leukocyte, lymphocyte, and neutrophil count were observed after V920. Dose-dependent humoral responses to V920 were noted at Day 28, as measured by GP-ELISA and PsVNA.

V920-006, V920-007, V920-008
Three Phase 1 open-label studies without placebo controls were included in the BLA. V920-006, V920-007, and V920-008 were reviewed. Immunogenicity data from these studies was generally consistent with findings observed in the blinded Phase 1. No new safety signals were identified in these studies.