EMADOC-1700519818-2258789
Committee for Medicinal Products for Human Use (CHMP)

Type II group of variations assessment report

Procedure No. EMA/VR/0000280470

Invented name: Ervebo

Common name: RECOMBINANT VESICULAR STOMATITIS VIRUS (STRAIN INDIANA) WITH A DELETION OF THE ENVELOPE GLYCOPROTEIN, REPLACED WITH THE ZAIRE EBOLAVIRUS (STRAIN KIKWIT-1995) SURFACE GLYCOPROTEIN

Marketing authorisation holder (MAH): Merck Sharp & Dohme B.V.

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Submission deadline	20 Jun 2025	19 Jun 2025
☐	Validation	7 Jul 2025	2 Jul 2025
☐	Start date	8 Jul 2025	8 Jul 2025
☐	CHMP Rapporteur AR	11 Aug 2025	8 Aug 2025
☐	PRAC Rapporteur AR	18 Aug 2025	11 Aug 2025
☐	PRAC comments	22 Aug 2025	22 Aug 2025
☐	CHMP comments	25 Aug 2025	25 Aug 2025
☐	Updated PRAC Rapporteur AR	26 Aug 2025	25 Aug 2025
☐	Updated CHMP Rapporteur AR	28 Aug 2025	28 Aug 2025
☐	PRAC outcome	2 Sept 2025	2 Sept 2025
☐	Start of CHMP written procedure	2 Sept 2025	2 Sept 2025
☐	CHMP Outcome	4 Sept 2025	4 Sept 2025
☐	Submission of responses	29 Sep 2025	29 Sep 2025
☐	Restart	30 Sep 2025	30 Sep 2025
☐	CHMP Rapporteur AR	03 Nov 2025	03 Nov 2025
☐	CHMP comments	17 Nov 2025	17 Nov 2025
☐	Updated CHMP Rapporteur AR	20 Nov 2025	21 Nov 2025
☐	Start of CHMP written procedure	25 Nov 2025	25 Nov 2025
☒	CHMP Outcome	27 Nov 2025	27 Nov 2025

Table of contents

1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 19 June 2025 an application for group of variations.

The following changes were proposed:

Variations requested		Type
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II
C.I.11.b	C.I.11.b Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment by the competent authority is required*	Variation type II

A grouped application consisting of: C.I.4: To update sections 4.4, 4.8, 5.1 of the SmPC to include safety and immunogenicity data following the results from study referred to as V920-015 ACHIV, listed as a category 3 study in the RMP; this is a Phase 2 Randomized, Multi-Center Double-Blind, Placebo-Controlled Study to evaluate the safety and immunogenicity of the V920/Ervebo (rVSVΔG-ZEBOV-GP) Ebola virus vaccine candidate in HIV-Infected adults and adolescents. The RMP version 2.1 has also been submitted. In addition, the Applicant took the opportunity to remove the complete list of local representatives, as suggested by the EMA during the review of specimens for the current ongoing renewal. Instead, the contact details of the MAH are included for ease of contact. C.I.11.b: Submission of an updated RMP version 2.1 in order to summarize the safety and effectiveness of Ervebo administered in the context of Expanded Access Protocol (EAP) 5 compassionate ring vaccination study.

The requested variation(s) proposed amendments to the Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

At the time of submission of the application, the PIP P/0315/2024 was completed.

The PDCO issued an opinion on compliance for the PIP P/0315/2024.

2. Overall conclusion and impact on the benefit/risk balance

Ervebo (V920 or rVSVΔG-ZEBOV-GP, live) is a single dose replication-competent attenuated live vaccine based on genetically engineered recombinant vesicular stomatitis virus (rVSV) vector, which has the gene encoding for the vesicular stomatitis virus (VSV) glycoprotein (GP) deleted from its RNA and replaced with the gene encoding for the Zaire Ebola Virus (ZEBOV) GP (rVSVΔG-ZEBOV-GP).

In the EU, Ervebo is indicated for active immunisation of individuals 1 year of age and older to protect against Ebola Virus Disease (EVD) caused by ZEBOV.

In this application, the MAH submitted the clinical study report (CSR) of clinical study V920-015, a Phase 2 Randomized, Multi-Center Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Immunogenicity of 1 or 2 doses of the V920 Ebola Virus Vaccine Candidate in adolescents and adults 13 to 70 years of age (inclusive) living with human immunodeficiency virus (HIV). Amendments to SmPC sections 4.4, 4.8 and 5.1 based on safety and immunogenicity results of study V920-015 are requested by the MAH.

This submission fulfils several obligations including the final study in the EU Paediatric Investigation Plan (PIP), the additional risk minimisation activity for immunocompromised individuals included in the Risk Management Plan (RMP), and the post authorisation measure (PAM) REC from Extension of indication procedure EMEA/H/C/004554/II/0025.

In study V920-015, adolescents and adults 13 to 70 years of age (inclusive) living with a controlled HIV infection (defined as individuals on antiretroviral therapy with undetectable HIV loads and CD4+ T cell counts above 200 cell/mm3) received either 1 or 2 doses of V920 or placebo. Participants were followed for humoral immune responses at different time-points (Day 28, Month 6 and Month 12 with additional time-points for those in the 2-dose group) and for safety through 1 year after vaccination (1 year after first vaccination for those in the 2-dose group). A total of 250 participants in Cohorts 1 to 5 (201 in the pooled V920 group, 49 in the pooled placebo group) were included in the immunogenicity and safety population (including in the V920 group: 52 adolescents and 149 adults; 100 females and 101 males).

Humoral immune response results of study V920-015 showed that administration of a single dose of V920 induces GP-specific binding and neutralizing antibody as observed at Day 28 post-vaccination in adolescents and adults living with a controlled HIV infection. At 1-year post-vaccination, antibody levels were still higher than pre-vaccination. Administration of a second dose of V920 at Day 56 after the primary dose resulted in a transient boost in binding and neutralizing antibody responses, which declined at Month 12 to levels comparable to those detected after a single primary dose. In the absence of immunological correlates of protection (ICP), the clinical relevance of those immunogenicity results is unknown.

Unexpected trends in the evolution over time of the measured binding and neutralizing antibody responses were noted, with higher antibody levels detected at later time-points. These unexpected trends in the evolution of antibody levels were also notable in other clinical studies, but they were more pronounced in study V920-015. The MAH stated that this might be related to the maturation of the immune response, which can result in a gradual increase or sustained elevation of antibody titres months after vaccination, even in the absence of additional antigen exposure.

In study V920-015, the safety profile of the V920 vaccine in 52 adolescents and 149 adults living with a controlled HIV infection was generally consistent with the known safety profile of Ervebo.

In the pooled V920 group (Cohorts 1 to 5 combined), the reported common injection-site adverse reactions reported within 14 days postvaccination (Vaccination 1 for Cohort 5) were injection-site pain (64.7%), swelling (5.5%), and erythema (4.5%). The reported systemic adverse reactions were headache (54.2%), fatigue (45.3%), feeling hot (25.4%), arthralgia (24.9%), myalgia (17.4%), chills (16.4%), nausea (13.9%), hyperhidrosis (12.9%), abdominal pain (12.4%), diarrhoea (8.5%), pyrexia (5.5%), rash (4%), and blister (1%). In the pooled V920 group, the frequencies of the reported solicited events specific to postvaccination within 42 days after vaccination were, overall, slightly higher than the frequencies observed 14 days after vaccination: arthralgia (28.9%), pyrexia (10.4%), rash (6%), and blister (1.5%). The frequencies observed after 1-year postvaccination (1 year after Vaccination 1 for Cohort 5) were similar to those at 42-days postvaccination (after Vaccination 1 for Cohort 5), and no clinically meaningful unsolicited event was reported.

Overall, no clinically meaningful differences in adverse event (AE) profiles were observed with safety analyses presented by subgroup by cohort (different CD4+ T cell counts in adults), by age category (adults or adolescents) and by sex (males or females). The results should be interpreted with caution due to the small sample sizes in the subgroups (by cohort around 40 vaccinated with V920 and 10 with placebo; 52 adolescents and 149 adults; 100 females and 101 males).

Concerning vaccine viraemia and shedding (saliva and urine), submitted results in terms of proportions of participants with viraemia or shedding at different time-points post-vaccination and quantitative data are

comparable between participants of V920-015 living with a controlled HIV infection and already available data from previous study conducted in HIV seronegative healthy individuals.

The benefit-risk balance of Ervebo remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variations approved		**Type**
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II
C.I.11.b	C.I.11.b Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment by the competent authority is required*	Variation type II

A grouped application consisting of: C.I.4: To update sections 4.4, 4.8, 5.1 of the SmPC to include safety and immunogenicity data following the results from study referred to as V920-015 ACHIV, listed as a category 3 study in the RMP; this is a Phase 2 Randomized, Multi-Center Double-Blind, Placebo-Controlled Study to evaluate the safety and immunogenicity of the V920/Ervebo (rVSVΔG-ZEBOV-GP) Ebola virus vaccine candidate in HIV-Infected adults and adolescents. The RMP version 3.0 has also been submitted. In addition, the Applicant took the opportunity to remove the complete list of local representatives, as suggested by the EMA during the review of specimens for the current ongoing renewal. Instead, the contact details of the MAH are included for ease of contact. C.I.11.b: Submission of an updated RMP version 3.0 in order to summarize the safety and effectiveness of Ervebo administered in the context of Expanded Access Protocol (EAP) 5 compassionate ring vaccination study.

☒is recommended for approval.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0315/2024 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIB and to the Risk Management Plan are recommended.

4. EPAR changes

The table in the 'Steps after' module of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Ervebo-H-C-004554-II-EMA/VR/0000280470'

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Ervebo (V920 or rVSVΔG-ZEBOV-GP, live) is a single dose replication-competent attenuated live vaccine based on genetically engineered rVSV vector, which has the gene encoding for the VSV GP deleted from its RNA and replaced with the gene encoding for the ZEBOV GP (rVSVΔG-ZEBOV-GP).

To date, Ervebo has been approved in the EU, the US, Canada, Switzerland, UK, and 11 African countries and it is prequalified by the WHO. In the EU, ERVEBO is indicated for active immunization of individuals 1 year of age and older to protect against EVD caused by Zaire Ebola virus, to be used in accordance with official recommendations.

Within this submission, the MAH submitted the CSR of clinical study V920-015, which fulfils several obligations including being the final study in the EU Paediatric Investigation Plan (EMEA-001786-PIP01-15-M03), addressing the RMP additional risk minimization activity for immunocompromised individuals, and fulfilling PAM REC from Extension of indication procedure EMEA/H/C/004554/II/0025: *"Results of V920-015 (CSR expected in 2024) should be submitted as soon as available".*

Within this procedure, the MAH also submitted a clinical overview summarizing the safety and effectiveness of V920 administered in the context of the Expanded Access Protocol 005 (EAP5) Compassionate ring vaccination study to evaluate the safety of the Ebola vaccine in the DRC from AUG-2018 through JUN-2020 in an outbreak setting.

This clinical overview was already submitted by the MAH within procedure EMEA/H/C/004554/REC025.1 in response to question 1 received from procedure EMEA/H/C/004554/REC/025. More specifically, in response to the request for submission of a comprehensive overview of effectiveness data (including a critical discussion of the available effectiveness data) including - as a minimum - all effectiveness data generated under V920-EAP5.

As specified in the cover letter, *study V920-EAP5, whilst already submitted to the EMA to fulfill PAM REC 23 (REC 025.1), is re-submitted to present and readdress the RMP additional pharmacovigilance activity for exposure during pregnancy/lactation*.

As no new effectiveness data was submitted, EAP5 effectiveness data are not addressed in section 6 of this AR.

Safety data from EAP5 - presented in the clinical overview that was already submitted in response to question 1 received from procedure EMEA/H/C/004554/REC/025 – were already summarized and discussed within procedure EMEA/H/C/004554/REC026.1. These are therefore not addressed in section 7 of this AR.

6. Clinical Immunogenicity aspects

6.1. Methods – analysis of data submitted

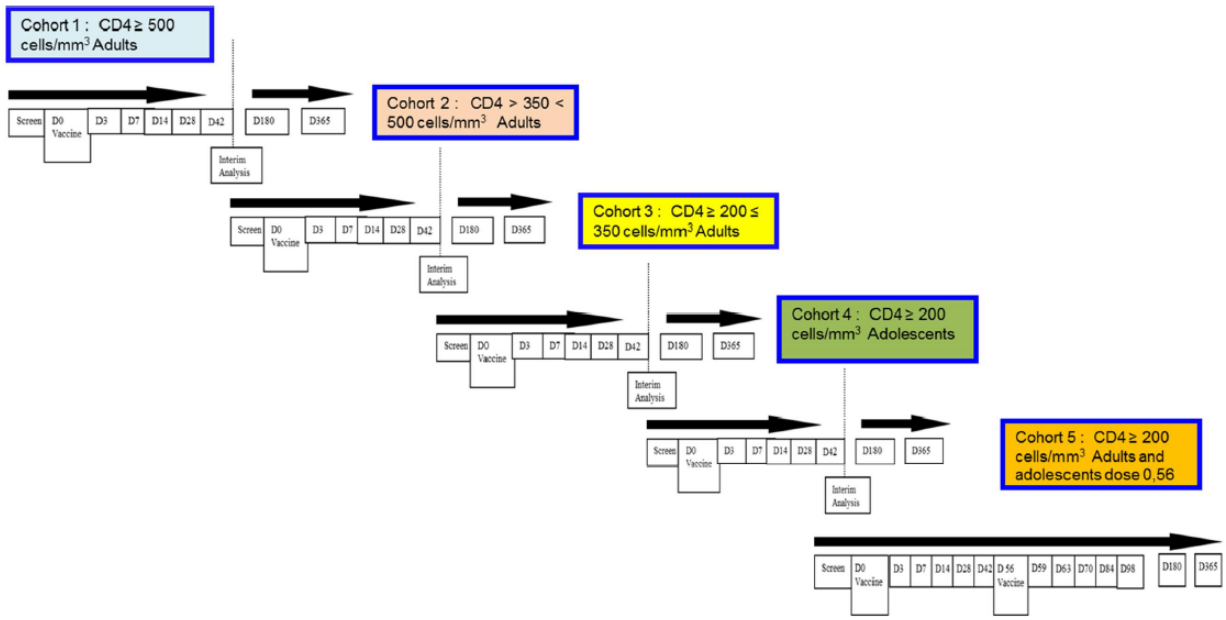
6.1.1. Study design

V920-015 is a Phase 2 Randomized, Multi-Center, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Immunogenicity of 1 or 2 doses of the V920 (rVSVΔG-ZEBOV-GP) Ebola Virus Vaccine Candidate in adolescents and adults 13 to 70 years of age (inclusive) living with HIV.

The study was conducted in Canada, Burkina Faso and Senegal.

The study was designed to enrol sequentially 5 study cohorts based on CD4+ T cell counts and age. A total of 50 adult (cohort 1 to 3), or adolescent (cohort 4) or adult and adolescent (cohort 5) participants was planned to be enrolled per cohort. Participants in Cohorts 1 to 4 were to be randomly assigned to receive 1 dose of V920 or placebo in a ratio of 4:1. Participants in Cohort 5 were to be randomly assigned to receive 1 dose of V920 or placebo in a ratio of 4:1 on Day 0, followed by booster vaccination at Day 56 (matching vaccine).

V920-015 study design is represented in Figure 1.



CD4=cluster of differentiation 4; D=Day
Note: Cohorts 1 to 4 (1-dose groups) received V920 or placebo at Day 0. Cohort 5 (2-dose group) received V920 or placebo on Day 0 and Day 56.

Figure 1: V920-015 Trial diagram

Blood samples for immunogenicity testing were obtained from all randomized participants in all cohorts at baseline (Day 0) before vaccination and at Day 28, Month 6, and Month 12. For the 2-dose group, blood samples were also collected at Days 56 (before Vaccination 2) and 84.

Safety and tolerability were assessed by clinical review of AEs and other relevant parameters (e.g. laboratory tests and vital signs) for all participants through 1-year postvaccination.

6.1.2. Study participants

Adolescents and adults with HIV-infection who were 13 to 70 (inclusive) years of age, on antiretroviral therapy with an undetectable viral load (<40 c/mL), had CD4 T-cell counts ≥200 cells/mm3, did not have a history of infection with a filovirus or VSV, and had not participated in a filovirus vaccine study or received a VSV-vectored vaccine, were eligible for the study.

Per protocol, enrolment was to be of ~100 subjects from 2 sites in Canada (Centre Hospitalier de l'Université de Montréal and Ottawa General Hospital) and of ~150 subjects from 2 sites in Africa (Centre MURAZ, Burkina Faso and Institut de Recherche en Santé, de Surveillance Epidémiologique et de Formations (IRESSEF), Dakar, Senegal).

Inclusion criteria

- HIV-infected adult or adolescent male or non-pregnant, non-breastfeeding female, ages 13 to 70 (inclusive) at the time of screening;
- On antiretroviral therapy with an undetectable viral load (<40 copies/mL);
- CD4 T-cell counts ≥200 cells/mm3;
- Written informed consent (subject or parent) and assent (adolescent), after reading the consent form and having adequate opportunity to discuss the study with an investigator or a qualified designee;
- Free of clinically significant health problems that could affect the safety of the participant, as determined by the Investigator by pertinent medical history and clinical examination prior to entry into the study;
- Available, able, and willing to participate for all study visits and procedures;
- Males and females who are willing to practice abstinence from sexual intercourse, or are willing to use effective methods of contraception, from at least 30 days prior to vaccination until 2 months after vaccination.

    a) If the partner is NOT of childbearing potential, the couple will only be required to use condoms, without other adjunctive contraception.

    b) For this study, a woman is considered of childbearing potential unless postmenopausal (≥ 1 year without menses) or surgically sterilized (tubal ligation, bilateral oophorectomy, or hysterectomy)

    c) Effective contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

        i. Male condoms PLUS
        ii. Oral contraceptives, either combined or progestogen alone
        iii. injectable progestogen
        iv. implants of etenogestrel or levonorgestrel
        v. oestrogenic vaginal ring
        vi. percutaneous contraceptive patches
        vii. intrauterine device or intrauterine system
- Be willing to minimize blood and body fluid exposure of others for 8 weeks after vaccination

    a. Avoiding the sharing of needles, razors, or toothbrushes
    b. Avoiding open-mouth kissing

Exclusion criteria

- History of prior infection with a filovirus or prior participation in a filovirus vaccine study;
- History of prior infection with VSV or receipt of a VSV-vectored vaccine;
- Presence of any febrile illness or any known or suspected acute illness on the day of any first immunization (subject may be rescheduled);
- Clinical manifestations of systemic diseases considered by the investigator to impact safety or immunogenicity;
- Receipt of systemic glucocorticoids (a dose ≥ 20 mg/day prednisone or equivalent) within one month, or any other cytotoxic or immunosuppressive drug within 12 months;

- Receipt of any investigational drug within 12 months of vaccination;
- Receipt of any live virus vaccine within 42 days prior to study entry or any other (non-live virus) vaccine within 14 days prior to study entry;
- History of sensitivity to any component of study vaccines per investigator brochure or package insert;
- Any baseline laboratory screening tests which is outside of acceptable range as defined in the protocol (local site reference ranges): ALT, AST, creatinine, hemoglobin, platelet count, total white blood cell count, urine protein, urine occult blood, urine glucose AND considered clinically significant by the clinical investigator. The following five screening parameters have limits set:
    a) absolute lymphocyte count ≥1000 cells/mm3
    b) hemoglobin not greater than 1.5 grams below the lower limit of the normal reference range at the local laboratory
    c) ALT, AST not greater than 2 to 2.5 times the upper limit at the local laboratory
    d) Platelet count ≥ 125,000 and ≤ 550,000
- To exclude transient laboratory abnormalities, the investigator may repeat a specific test (E.g. hemoglobin) once during the screening period (I.e. a maximum of two tests), , and if the repeat test is normal, subject may be enrolled;
- Have an active malignancy or history of metastatic or hematologic malignancy except non-melanoma skin cancers;
- Suspected or known alcohol and/or illicit drug abuse within the past 5 years;
- Moderate or severe illness and/or fever >101°F (38.3ºC) orally or > 100°F (37.8ºC) axillary within one week prior to vaccination;
- Pregnant or breastfeeding female, or female who intends to become pregnant during the study period;
- Administration of immunoglobulins and/or any blood products within the 120 days preceding study entry or planned administration during the study period;
- Any other significant finding that in the opinion of the investigator would increase the risk of the individual having an adverse outcome from participating in this study.

6.1.3. Study interventions

Per Protocol, one dose of ≥2 x 10E7 pfu of the study vaccine or placebo was to be administered at D0 in all Cohorts. In Cohort 5, a second dose of matching vaccine (≥2 x 10E7 pfu/ml) or placebo was to be administered at Day 56. Vaccination was to be given on the day of treatment allocation/randomization or as close as possible to the date on which the subject is allocated/assigned. Study interventions are summarized in Table 1.

Table 1: Trial Treatment/Vaccination

Vaccine	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use
V920	≥2x10^7 PFU in 1mL	Once in cohorts 1-4/Twice in Cohort 5	IM	Visit 1, D0 and Visit 7 (Day 56), where applicable	Experimental
Normal saline (0.9%)	1 ml	Once in cohorts 1-4/Twice in Cohort 5	IM	Visit 1, D0 and Visit 7 (Day 56), where applicable	Placebo-control
Subjects in Cohort 5 will receive two doses of V920 ≥2x10^7 PFU or two doses of normal saline placebo (0.9%) on D0 and D56.					

Information for the V920 vaccine lots provided by the MAH and administered in Study V920-015 is provided in a table submitted in response to RSI to the CHMP comment 2 (Table 2). Distribution of the product by cohort was not submitted (would require manual review, extraction, compilation and validation of source documentation in the different clinical sites, not pursued). It appears that 3 different V920 Drug Product Lots were used in study V920-015, all had a potency ≥2 x 10E7 pfu/mL.

Placebo was sterile normal saline (sodium chloride 0.9% for injection, US Pharmacopeia, preservative free).

Table 2: V920 drug lot numbers, actual potencies, and country each lot was shipped to

Lot Number	Potency[1]	Country Vaccine Shipped To
WL00067464 (underlying drug product lot WL00063635)	1.3 x 10^8 pfu/mL	Burkina Faso, Senegal
0000852249 (underlying drug product lot WL00067929)	3.0 x 10^8 pfu/mL	Burkina Faso, Senegal, Canada
WL00061392 (underlying drug product lot WL00061283)	5.4 x 10^7 pfu/mL	Canada
[1] Per Certificate of Analysis at release		

6.1.4. Prior and Concomitant medications

Prior medication taken by the subject within 6 months before dose of trial vaccination and medication taken by the subject during the trial were to be recorded.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

Listed below are specific restrictions for concomitant therapy or vaccination following each vaccination:

1. Systemic glucocorticoids (a dose ≥ 20 mg/day prednisone or equivalent) within one month, or any other cytotoxic or immunosuppressive drug within twelve months;

2. Any investigational drug within twelve months;

3. Any live virus concomitant vaccinations within 42 days;

4. Any other (non-live) concomitant vaccinations within 14 days.

6.1.5. Objectives and endpoints

The objectives, hypotheses, and endpoints are provided in Table 3.

Table 3: V920-015 objectives, hypotheses and endpoints

Primary Objectives	Primary Endpoints
• Evaluate the safety and tolerability of V920 in HIV-infected adults and adolescents.	• Solicited local and systemic AEs for 14 days after each vaccination • Fever, arthritis, arthralgia, rash, and blisters/vesicular lesions for 42 days after each vaccination • Unsolicited AEs for 42 days after each vaccination • Vaccine-related SAEs through to Day 365 • Changes in vital signs (eg, blood pressure, heart rate, respiratory rate, and temperature) • Changes in clinical laboratory values
• Evaluate the immunogenicity of V920 via ZEBOV-specific antibody responses induced by V920 in HIV-infected adults and adolescents. Hypotheses: The GMT of GP-ELISA in V920 vaccinated HIV-infected adults and adolescents will be superior to the GMT of the GP-ELISA in placebo vaccinated HIV-infected adults and adolescents at Day 28 in Cohorts 1 to 5 combined. The GMT of GP-ELISA in V920 vaccinated HIV-infected adults and adolescents will be superior to the GMT of the GP-ELISA in placebo vaccinated HIV-infected adults and adolescents Day 28 after the last dose of vaccine (equivalent to Day 84 from first dose) in Cohort 5.	• GMTs at Day 28 after randomization (initial vaccination) in Cohorts 1 to 5 combined, as measured by GP-ELISA • GMTs at Day 28 after last dose of vaccine, as measured by GP-ELISA (Cohort 5)

Secondary Objectives	Secondary Endpoints
• Evaluate ZEBOV-specific antibody responses induced by V920 through Day 180 (Month 6) and Day 365 (Month 12).	• GMTs, GMFIs, and seroresponse rates through 1-year postvaccination in Cohorts 1 to 5, as measured by GP-ELISA and PRNT
• Evaluate the safety and tolerability of 2 doses of V920 in HIV-infected adults and adolescents administered 56 days apart.	• Solicited local and systemic AEs for 14 days after each vaccination • Fever, arthritis, arthralgia, rash, and blisters/vesicular lesions for 42 days after each vaccination • Unsolicited AEs for 42 days after each vaccination • Vaccine-related SAEs through to Day 365 • Changes in vital signs (eg, blood pressure, heart rate, respiratory rate, and temperature) • Changes in clinical laboratory values
• Evaluate the immunogenicity of 2 doses of V920 administered 56 days apart via ZEBOV-specific antibody responses induced by V920 at Day 28 post-dose 2 in HIV-infected adults and adolescents.	• GMTs, GMFIs, and seroresponse rates at Day 28 post-dose 2 in Cohort 5, as measured by GP-ELISA and PRNT
• Evaluate VSV viremia and shedding after administration of V920.	• Vaccine viral shedding
• Evaluate the impact of V920 on HIV viral load, CD4 counts, and CD4/CD8 ratio.	• Changes in clinical laboratory values

There were also tertiary objectives specified in the Protocol V4.0 (dated 17 September 2019), but not in SAP. These are: (1) Evaluate Ebola-specific CD8+ T cell responses; (2) Evaluate B-cell repertoire; (3) Evaluate the impact of V920 on HIV viral reservoir.

Based on CSR, none of these tertiary objectives were explored.

6.1.6. Immunogenicity assessment

For immunogenicity assessment, samples were tested at 2 locations in the US.

Immunogenicity results reported in V920-015 were generated from a validated proprietary glycoprotein enzyme-linked immunosorbent assay GP-ELISA and a validated plaque reduction neutralization test (PRNT).

Both GP-ELISA and PRNT assays are described below based on the information provided in the SAP.

Differently from other studies conducted previously, samples collected from participants from African sites were not gamma irradiated.

Sample handling

Participants in Cohorts 1 to 4 (1-dose group) had immunogenicity serology samples collected at baseline and Day 28, Month 6, and Month 12 postvaccination.

Participants in Cohort 5 (2-dose group) had immunogenicity serology samples collected at baseline and Day 28, Day 56, Day 84, Month 6, and Month 12 after Vaccination 1. Samples starting at Day 56 are after Vaccination 2 for this 2-dose group.

Blood collection time points and day ranges - as specified in the SAP – are listed in Table 4.

Table 4: Blood Collection Time Points

Time Points and Day Ranges	V920-007 Children 6-17 Years of Age	V920-013	V920-014[a]	V920-015 Cohort 1-4	V920-015 Cohort 5
Baseline	<D0	D0	D0	<D0	<D0
Day 1			D1		
Day 2 or 3			D2 or D3		
Day 7	D7		D7		
Day 14	D14		D14		
Day 28 / Month 1	D28 ±7	M1 ±7	D28 ±7	D28 ±3	D28 ±3
Day 56	D56 ±7		D56 ±7		D56 ±3
Day 84 / Month 3	D84 ±7	M3 ±7	D84 ±7		D56+28 ±3
Day 180 / Month 6	D180 ±14	M6 ±14	D180 ±14	D180 ±14	D180 ±14
Day 365 / Month 12	D365 ±14	M12 ±14	D365 ±14	D365 ±28	D365 ±28
Month 18		M18 ±14			

Description of Assay Methods

Zaire ebolavirus (ZEBOV) Anti-Glycoprotein (GP) Immunoglobulin G (IgG) Human Enzyme-Linked Immunosorbent Assay (GP-ELISA)

To measure and quantify total IgG antibodies against V920, an indirect GP-ELISA which utilizes a purified recombinant Ebola Zaire glycoprotein (rGP) as the coating antigen has been validated. Briefly, microtiter plates are coated with purified recombinant ZEBOV-rGP. Serum samples and controls are then incubated with the rGP coated wells allowing ZEBOV-GP specific antibodies to bind. A serial diluted reference standard, obtained from a pool of vaccinated human donors, is also included. Each well is then incubated with goat anti-human IgG horseradish peroxidase conjugate, which enzymatically reacts with the tetramethylbenzidine substrate to form a coloured solution. After incubation, the enzymatic reaction is stopped using a sulfuric acid solution. The optical density (OD) is measured on an ELISA plate reader and serum sample titer concentrations are calculated from the standard curve using a 4-parameter logistic (4PL) curve fit. Titers are reported as GP-ELISA units/mL (EU/mL).

rVSVΔG-ZEBOV-GP Plaque Reduction Neutralization Test PRNT ($PRNT_{60}$)

A PRNT assay has been validated to determine the neutralizing antibody levels in human sera following the administration of V920. In this assay, serum is diluted from 1:5 to 1:10,240 and mixed with an equal volume of diluted V920 for final dilutions of 1:10 to 1:20,480. Neutralization is allowed to proceed over an 18-hour period at 2-8ºC after which the serum/virus mixture is used to inoculate Vero cells

monolayers. Viral adsorption is done at 37±2ºC for 60 minutes followed by a methylcellulose overlay. The infected cells are incubated at 37±2ºC for 2 days. Plaques are visualized by crystal violet stain and are counted using the ViruSpot from Autoimmun Diagnostika GMBH (AID). Determination of the $PRNT_{60}$ is based on inverse of serum sample dilution that reduced viral plaques by 60% compared to virus control.

Lower Limits of Quantification (LLOQ) are provided in Table 5. Immunogenicity values below LLOQ (<LLOQ) were imputed as LLOQ/2.

Table 5: Lower Limits of Quantification (LLOQ) of the Validated Assays

Assay	LLOQ
GP-ELISA (EU/mL)	36.11
PRNT	35

6.1.7. Sample size

For immunogenicity assessment, there is 80% power to detect a Geometric Mean Ratio (GMR) of 1.6 (V920 GP-ELISA GMT of 58 EU/mL vs. Placebo GP-ELISA GMT of 36 EU/mL, the lower limit of quantification [LLOQ]) and 90% power to detect a GMR of 1.7 (V920 GP-ELISA GMT of 62 EU/mL) if comparing all five cohorts (N=200 V920 vs. N=50 Placebo) combined. This power analysis assumes a 10% dropout, a standard deviation of 1 on the log scale, and a 2-sided 5%.

There is 80% power to detect a GMR of 2.9 (V920 GP-ELISA GMT of 105 EU/mL) and 90% power to detect a GMR of 3.4 (V920 GP-ELISA GMT of 124 EU/mL) if comparing each cohort independently (N=40 V920 vs. N=10 Placebo). This power analysis assumes a 10% dropout, a standard deviation of 1 on the log scale, and a 2-sided 5%.

For safety assessment, there is 80% power to detect a 12% difference in event rates that occur with a frequency of 1% in the control group if comparing four cohorts (N=200 V920 vs. N=50 Placebo) combined and a 46% difference if comparing each cohort independently (N=40 V920 vs. N=10 Placebo).

6.1.8. Randomization, blinding and stratification

According to V920-015 Protocol Version 4.0, the study is a double-blind trial, and Sponsor, investigator, and subject will not know the vaccine administered until unblinding. Unblinding will be performed after the database is locked.

A participant may be unblinded during the course of the study if the PI deems that, for health purposes, the blind must be broken. Only in the case of an emergency, when knowledge of whether the participant has received the investigational product is essential for the clinical management or welfare of the participant, the investigator may authorize the unblinding of a participant's treatment assignment. If time permits, the investigator or qualified study staff designee is encouraged to contact the Sponsor coordinating PI, prior to breaking the blind.

Subjects were to be assigned randomly according to a computer-generated allocation schedule.

Participants were to be randomized 4:1 (study vaccine: placebo control) using centralized randomization, with a total of approximately 200 study vaccine recipients and 50 placebo control recipients.

To satisfy the requirement that each site enrolls at least one placebo subject in each cohort, enrollment had to proceed until treatments have been randomized to at least one complete block of subjects (consisting of four subjects receiving treatment and one receiving placebo) at each site.

Treatment allocation/randomization was to be stratified by the 5 cohort groups:

- Cohort 1: Screening CD4 cell counts for adults: CD4 cells/mm3 ≥500
- Cohort 2: Screening CD4 cell counts for adults: CD4 cells/mm3 >350 and <500
- Cohort 3: Screening CD4 cell counts for adults: CD4 cells/mm3 ≥200 and ≤350
- Cohort 4: Screening CD4 cell counts for adolescents, age 13 to 17: CD4 cells/mm3 ≥200
- Cohort 5: Screening CD4 cell counts for adults and adolescents, age 13 to 17: CD4 cells/mm3 ≥ 200 with 2 doses.

All cohorts are stratified by site (two sites per cohort).

Cohort 5 was to be stratified by site, and by age group (adolescent vs. adult). Once three blocks of five adolescents have been enrolled, with at least one block at each site, the requirement to enroll at least 12 adolescents in Cohort 5 will be met.

6.1.9. Statistical methods

The MAH submitted a Statistical Analysis Plan outlining the statistical analysis strategy and procedures for the V920-007, V920-013, V920-014, and V920-015 studies. Based on revision dates, the submitted SAP is dated 27 September 2024, which is prior to the MSD Database Lock Date specified in the V920-015 CSR (17 October 2024).

Analysis populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study vaccination. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who received incorrect study vaccine will be included in the treatment group corresponding to the study vaccine actually received.

The Per-Protocol population (PP) will serve as the primary population for the analysis of immunogenicity data in this study. The Per-Protocol population excludes subjects due to important deviations from the protocol that may substantially affect the results of the primary immunogenicity endpoint(s). For example, subjects who are seropositive at baseline will be excluded from the Per-Protocol population. All subjects who meet the inclusion criteria, were seronegative at baseline, and do not have a major protocol deviation will be included in the per-protocol analysis.

The final determination of subjects with major protocol deviations, and thereby the composition of the Per-Protocol population, will be made prior to the unblinding of the database for the primary CSR and will be documented in a separate memo.

A supportive analysis using the Full Analysis Set (FAS) population may be performed. The FAS population consists of all randomized subjects with serology data.

Immunogenicity Analyses

Immunogenicity will be summarized as follows:

- The immunogenicity population will be the Per-Protocol (PP) population or the Full Analysis Set (FAS) population depending on if the PP population can be defined from the data received.
- Immunogenicity summaries for the GP-ELISA and PRNT may include:
    - Geometric Mean Titers (GMT);
    - Geometric Mean Fold Increase (GMFI) from baseline;
    - Seroresponse at any time during study and for each timepoint defined as:
        - GP-ELISA:
            - Primary: 2-fold increase from baseline and ≥200 EU/mL
            - Secondary: 4-fold increase from baseline
        - PRNT: 4-fold increase from baseline

For V920-015, hypotheses comparing GMTs between V920 to placebo in HIV-infected participants at Day 28 will be tested using ANOVA and a two-sided test at α = 0.05. The statistical criterion for successful demonstration of superiority requires the lower bound of the 2-sided 95% CI on the GMT ratio [V920 / Placebo] to be >0.

No multiplicity adjustments were planned to be made. Generally, missing data were not imputed.

Summaries for some analyses are provided for the following subgroups:

- Age category (adolescents, adults);
- Male and Female;
- Africa and ex-Africa;
- Baseline GP-ELISA <200 EU/mL and baseline GP-ELISA ≥200 EU/mL.

Safety Analyses

Safety and tolerability will be summarized as follows:

- The safety population will be the All Participants as Treated (APaT) population.
- Safety and tolerability will be assessed by clinical review of adverse events (AEs) and other relevant parameters (e.g., vaccine viral shedding, laboratory tests and vital signs)

Safety summaries will include counts and percentages of subjects with AEs and other relevant safety outcomes. For continuous safety measures summary statistics for baseline, on-treatment, and change from baseline values will be provided if relevant data are received.

Changes from protocol-specified analyses

The following changes to the planned analyses were not previously described in a protocol amendment or SAP revision:

- The SAP stated that the CD4/CD8 ratio would be evaluated if relevant data were received. The CD4/CD8 ratio was not evaluated because CD8 data were not received.
- The SAP stated that the LLOQ for PRNT is 35. For measurements below the LLOQ, ½ LLOQ was planned to be used for the calculation of GMT, fold-rise, and seroresponse.

In the data received, PRNT measurements less than the LLOQ and above the LLOD (20) were reported. Ten measurements ranging from 21 to 35 were included in the dataset. These 10 measurements were analyzed using their actual values. Measurements labeled "<LLOQ" were analyzed as ½ LLOQ (½ x 35).

No changes were made after study unblinding.

6.2. Results

6.2.1. Conduct of the study

The original V920-015 study protocol was amended 5 times.

Based on amendment history as specified in CT14B_ACHIV-Ebola Protocol Version 4.0, protocol version 2.7 (11-MAY-2017) was active at the start of recruitment (first participant first visit dated 01-NOV-2017). Subsequent amendments had an impact on applied inclusion/exclusion criteria. In protocol version 3.0 (10-JAN-2018) inclusion age was increased to 70 years of age and exclusion of healthcare workers was removed. In protocol version 4.0 (17-SEP-2019), exclusion criteria were revised to allow enrolment of participants with screening hematologic and chemistry values outside of normal site reference ranges, if deemed not clinically significant by the clinical investigator; laboratory sample collections were revised, and protocol was amended to clarify that a participant who is not eligible for an earlier cohort may be screened for eligibility for a subsequent cohort.

6.2.2. Participant flow and numbers analysed

First participant first visit was on 01-NOV-2017 and last participant last visit was on 03-MAR-2023. The analyses presented in the submitted CSR (revised report date 16 May 2025) are based on a database lock dated 17-OCT-2024.

Participant disposition

In total (Cohorts 1 to 5 combined), 251 participants were randomized (202 in the V920 group, 49 in the placebo group) in study V920-015 across 4 study sites in 3 countries. All randomized participants received at least 1 dose of study intervention, except 1 V920 participant in Cohort 1 who was randomized but not vaccinated and discontinued the study.

Three participants (2 participants in Cohort 1 and 1 participant in Cohort 2) discontinued the study due to loss to follow-up.

The majority of the participants were randomized at the site in Burkina Faso (152/251; 60.6%), 73/251 (29.1%) were randomized at the site in Senegal and 26/251 (10.4%) in Canada (Table 14.1-7 of CSR). This is different from what originally planned per protocol. Namely planned enrolment was of ~100 subjects from Canadian sites and of ~150 subjects from African sites.

Numbers analysed

A total of 250 participants in Cohorts 1 to 5 (201 in the pooled V920 group, 49 in the pooled placebo group) were included in the immunogenicity and safety populations (Table 6 and Table 7). The participant randomized but not vaccinated was excluded from the immunogenicity and safety analyses.

Participants Accounting for the GP-ELISA Per-Protocol Immunogenicity Population by Vaccination Group for All Randomized or Enrolled Participants of Cohort 1 to Cohort 5 are summarized in Table 6.

Participants Accounting for the PRNT Per-Protocol Immunogenicity Population by Vaccination Group for All Randomized or Enrolled Participants of Cohort 1 to Cohort 5 are summarized in Table 7.

No participant was excluded from the Per Protocol population due to a protocol deviation.

In the 1-dose V920 group (Cohorts 1 to 4 combined) 3 participants were missing baseline serology samples for the GP-ELISA analyses and 2 participants were missing Month 12 serology samples for the GP-ELISA and PRNT analyses.

In the placebo group (Cohorts 1 to 5 combined), one participant was missing Day 28 serology and one participants was missing Month 12 serology (both for GP-ELISA and PRNT analyses).

Table 6: Participants Accounting for the GP-ELISA Per-Protocol Immunogenicity Population by Vaccination Group (All Randomized or Enrolled Participants - Cohort 1 to Cohort 5)

	V920 1 Dose[a] (N=162)	V920 2 Dose[b] (N=40)	Pooled V920[c] (N=202)	Placebo[c] (N=49)
Participants Vaccinated[d]	**161**	**40**	**201**	**49**
Reasons for Exclusion From the Per-Protocol Immunogenicity Population	**1**		**1**	
Participants not Vaccinated	1	0	1	0
Protocol Violation	0	0	0	0
Included in Per-Protocol Immunogenicity Population for GP-ELISA (EU/ml)	**161**	**40**	**201**	**49**
Missing Serology Samples/Results at Each Time Point[e]				
Day 0 (Baseline)	3	0	3	0
Day 28	0	0	0	1
Day 56[f]	161	0	161	39
Day 84[f]	161	0	161	39
Month 6	0	0	0	1
Month 12	2	0	2	2

[a] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.
[b] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose.
[c] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose.
[d] Participants who did not receive an injection were excluded from all analysis populations.
[e] Participants are counted once in each applicable exclusion category. A participant may appear in more than one category.
[f] Cohort 5 Adults and adolescents CD4≥200 2 dose.
N=number of participants randomized to the respective vaccination group.
GP-ELISA=glycoprotein enzyme-linked immunosorbent assay.

Table 7: Participants Accounting for the PRNT Per-Protocol Immunogenicity Population by Vaccination Group (All Randomized or Enrolled Participants - Cohort 1 to Cohort 5)

	V920 1 Dose[a] (N=162)	V920 2 Dose[b] (N=40)	Pooled V920[c] (N=202)	Placebo[c] (N=49)
Participants Vaccinated[d]	**161**	**40**	**201**	**49**
Reasons for Exclusion From the Per-Protocol Immunogenicity Population	**1**		**1**	
Participants not Vaccinated	1	0	1	0
Protocol Violation	0	0	0	0
Included in Per-Protocol Immunogenicity Population for PRNT	**161**	**40**	**201**	**49**
Missing Serology Samples/Results at Each Time Point[e]				
Day 0 (Baseline)	0	0	0	0
Day 28	0	0	0	1
Day 56[f]	161	0	161	39
Day 84[f]	161	0	161	39
Month 6	0	0	0	1
Month 12	2	0	2	2

[a] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.
[b] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose.
[c] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose.
[d] Participants who did not receive an injection were excluded from all analysis populations.
[e] Participants are counted once in each applicable exclusion category. A participant may appear in more than one category.
[f] Cohort 5 Adults and adolescents CD4≥200 2 dose.
N=number of participants randomized to the respective vaccination group.
PRNT=plaque reduction neutralization test.

Protocol deviations

Important protocol deviations were reported for 15 participants. No participant's data were excluded from analysis due to a protocol deviation. No protocol deviations were classified as a serious GCP compliance issue.

6.2.3. Baseline data

Demographics and Baseline Disease Characteristics for all participants randomized in all 5 cohorts combined are summarized in Table 8.

Relatively to the overall characteristics of the participants in all 5 cohorts:

- The majority of the participants were randomized at the site in Burkina Faso (152/251; 60.6%), 73/251 (29.1%) were randomized at the site in Senegal and 26/251 (10.4%) in Canada.
- The majority had a baseline GP-ELISA <200 EU/mL (91.6%).
- The majority had CD4 ≥500 cells/mm3 (52.2%), the remaining participants were evenly distributed among participants with CD4 T cell counts ranging from 350-500 cells/mm3 (25.5%) and participants with CD4 T cell counts ranging from ≥200 to ≤350 cells/mm3 (22.3%).
- There were 65/251 (25.9%) participants aged 13-17 years, 103/251 (41%) aged 18-49 years, 63/251 (25.1%) aged 50-59 years, 18/251 (7.2) aged 60-65 years and 2/251 (0.8%) aged >65 years. Proportions of participants with these age ranges were comparable in the arms.
- Similar proportions of male and female were recruitment, but there was a higher proportion of male participants who received V920 (50.5%) compared with placebo (38.8%), and a lower proportion of females who received V920 (49.5%) compared with placebo (61.2%).

Demographic characteristics by cohort were presented in the CSR. When considering the characteristics of participants of cohort 4 (Adolescents CD4 T cell counts ≥200 cells/mm3, 1 Dose) and of cohort 5 (Adults

and Adolescents CD4 T cell counts ≥200 cells/mm3, 2 Dose), it is noted that the majority had a CD4 T cell counts ≥500 cells/mm3 (43/50 (86%) in cohort 4 and 37/50 (74%) in cohort 5).

Table 8: Participant Characteristics (All Participants Randomized, Cohort 1 to Cohort 5)

	V920		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	202		49		251	
Sex						
Male	102	(50.5)	19	(38.8)	121	(48.2)
Female	100	(49.5)	30	(61.2)	130	(51.8)
Age (Years)						
13 to 17	52	(25.7)	13	(26.5)	65	(25.9)
18 to 49	83	(41.1)	20	(40.8)	103	(41.0)
50 to 59	50	(24.8)	13	(26.5)	63	(25.1)
60 to 65	15	(7.4)	3	(6.1)	18	(7.2)
>65	2	(1.0)	0	(0.0)	2	(0.8)
Mean	39.1		38.1		38.9	
SD	16.8		16.9		16.7	
Median	44.0		41.0		44.0	
Range	13 to 70		13 to 65		13 to 70	
Race						
Black Or African American	181	(89.6)	44	(89.8)	225	(89.6)
Multiple	0	(0.0)	1	(2.0)	1	(0.4)
Asian, White	0	(0.0)	1	(2.0)	1	(0.4)
White	21	(10.4)	4	(8.2)	25	(10.0)
Ethnicity						
Not Hispanic Or Latino	202	(100.0)	48	(98.0)	250	(99.6)
Missing	0	(0.0)	1	(2.0)	1	(0.4)
Country						
Burkina Faso	122	(60.4)	30	(61.2)	152	(60.6)
Canada	21	(10.4)	5	(10.2)	26	(10.4)
Senegal	59	(29.2)	14	(28.6)	73	(29.1)
Cohort						
Cohort 1: Adult - CD4≥500 cells/mm³	41	(20.3)	10	(20.4)	51	(20.3)
Cohort 2: Adult - CD4 >350 cells/mm³ and <500 cells/mm³	40	(19.8)	10	(20.4)	50	(19.9)
Cohort 3: Adult - CD4 ≥200 cells/mm³ and ≤350 cells/mm³	41	(20.3)	9	(18.4)	50	(19.9)
Cohort 4: Adolescent - CD4≥200 cells/mm³	40	(19.8)	10	(20.4)	50	(19.9)
Cohort 5: Adolescent - CD4≥200 cells/mm³	12	(5.9)	3	(6.1)	15	(6.0)
Cohort 5: Adult - CD4≥200 cells/mm³	28	(13.9)	7	(14.3)	35	(13.9)
Baseline GP-ELISA (EU/mL)						
<200	183	(90.6)	47	(95.9)	230	(91.6)
≥200	15	(7.4)	2	(4.1)	17	(6.8)
Missing	4	(2.0)	0	(0.0)	4	(1.6)
CD4 (cells/mm³)						
≥500	104	(51.5)	27	(55.1)	131	(52.2)
>350 and <500	52	(25.7)	12	(24.5)	64	(25.5)
≥200 and ≤350	46	(22.8)	10	(20.4)	56	(22.3)
CD4 (cells/mm³)						
Participants with data	202		49		251	
Mean	597.8		650.5		608.1	
SD	294.6		473.5		336.5	
Median	514.5		566.0		518.0	
Range	205 to 1580		230 to 3087		205 to 3087	
Height (cm) at Randomization						
Participants with data	202		49		251	
Mean	166.5		165.2		166.3	
SD	10.7		10.2		10.6	
Median	166.9		165.0		166.1	
Range	136 to 192		135 to 186		135 to 192	
Weight (kg) at Randomization						
Participants with data	202		49		251	
Mean	63.2		63.1		63.2	
SD	17.6		14.8		17.1	
Median	62.0		64.5		62.6	
Range	29 to 114		25 to 91		25 to 114	
BMI (kg/m²) at Randomization						
Participants with data	202		49		251	
Mean	22.6		22.9		22.7	
SD	5.5		4.4		5.3	
Median	21.5		22.8		22.0	
Range	13 to 42		14 to 34		13 to 42	

SD=Standard deviation.
BMI=body mass index (kg/m²); CD4=cluster of differentiation 4 (cells/mm³); HIV=human immunodeficiency virus.

Reported medical history conditions for all 5 cohorts were generally comparable between the intervention groups. Reported concomitant medications for all 5 cohorts were generally comparable between the intervention groups. All participants received antivirals for systemic use.

6.2.4. Outcomes and estimation

Immunogenicity analyses were presented for cohorts 1 to 5 combined and also by cohorts and by subgroup for the following categories: age category (adult or adolescent), sex, baseline GP-ELISA, and country at randomization.

Immunogenicity Results - GP-ELISA

Superiority Analyses

1 Dose

In Cohorts 1 to 5 combined, the GP-ELISA estimated GMT at Day 28 post-vaccination (after Vaccination 1 for Cohort 5) was superior in the V920 group compared with the placebo group, with an estimated fold difference of 42.90 (95% CI: 31.49, 58.43; p<0.001) – *Table 9*.

Table 9: Statistical Analysis of Superiority of V920 vs. Placebo for the GP-ELISA GMT Measured at Day 28 Postvaccination (GP-ELISA Per-Protocol Immunogenicity Population - Cohort 1 to Cohort 5)

Assay	Comparison Group A vs. Comparison Group B	Comparison Group A N	Comparison Group A n	Comparison Group A Estimated GMT[a] (EU/mL)	Comparison Group B N	Comparison Group B n	Comparison Group B Estimated GMT[a] (EU/mL)	Estimated Fold Difference Group A / Group B (95% CI)	p-value	Conclusion
GP-ELISA	V920 vs. Placebo	201	201	1,223.1	49	48	28.5	42.90 (31.49, 58.43)	<0.001	Superiority is met
Overall conclusion: The superiority criteria were met.										

The per-protocol population consists of all vaccinated participants with serology data and did not violate inclusion/exclusion criteria.
V920 consists of:
V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.
V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose. For Cohort 5, GMT is presented at Day 28 postvaccination 1.
[a] Based on an ANOVA model with a response of the natural log of individual titers and fixed effects for intervention group.
N=number of participants with serology data at one or more timepoints according to the intervention to which they were randomized.
n=number of participants with serology data at Day 28.
CI=confidence interval; GP-ELISA=anti-glycoprotein human enzyme-linked immunosorbent assay (EU/mL); GMT=geometric mean titer.

2 Doses

In Cohort 5, the GP-ELISA estimated GMT at Day 28 after the last dose of vaccine (equivalent to Day 84 after Vaccination 1) was superior in the V920 group compared with the placebo group, with an estimated fold difference of 208.66 (95% CI: 115.57, 376.72; p<0.001). Estimated GMTs (based on an ANOVA model with a response of the natural log of individual titres and fixed effects for intervention group) was of 8,416.0 EU/mL in the V920 group and of 40.3 EU/mL in the placebo group.

Summary of GP-ELISA Geometric Mean Titers

The GP-ELISA GMTs for the 1-dose V920 (Cohorts 1 to 4 combined) and the 2-dose V920 (Cohort 5) groups are shown in Table 10.

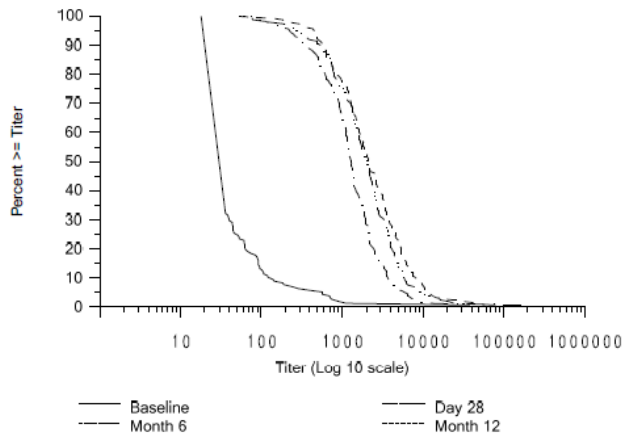
Data indicate that:

- GMTs increased post-vaccination and remained elevated through Month 12. An unexpected trend of an increase in GMTs at Month 6 and Month 12 as compared to Day 28 GMT in the V920 1-dose group is noted. This trend is also visualized in the submitted reverse cumulative distribution curves (Figure 2).
- Post-vaccination GMTs were higher than those of the pooled placebo group at all timepoints after baseline.
- The GP-ELISA GMTs for the 2-dose V920 group (Cohort 5) peaked at Day 84 and decreased to comparable concentrations as the 1-dose V920 group (Cohorts 1 to 4 combined) at Month 6 (higher GMT in the 2-dose group as compared to Month 6 GMT in the V920 1-dose group, but with overlapping 95% CI) and at Month 12.

Table 10: Summary of Geometric Mean Titres (GP-ELISA Per-Protocol Immunogenicity Population - Cohort 1 to Cohort 5)

Assay Time Point	V920 1 Dose[a] (N=161) GMT (n) [95% CI]	V920 2 Dose[b] (N=40) GMT (n) [95% CI]	Pooled V920[c] (N=201) GMT (n) [95% CI]	Placebo[c] (N=49) GMT (n) [95% CI]
GP-ELISA				
Baseline	33.2 (158) [28.1, 39.3]	40.6 (40) [29.1, 56.5]	34.6 (198) [29.8, 40.2]	28.3 (49) [21.0, 38.2]
Day 28	1,231.1 (161) [1,057.6, 1,433.0]	1,191.8 (40) [878.7, 1,616.3]	1,223.1 (201) [1,068.0, 1,400.9]	28.5 (48) [21.6, 37.7]
Day 56[b]		1,469.0 (40) [1,122.3, 1,923.0]	1,469.0 (40) [1,122.3, 1,923.0]	32.8 (10) [19.2, 56.3]
Day 84[b]		8,416.0 (40) [6,461.9, 10,961.1]	8,416.0 (40) [6,461.9, 10,961.1]	40.3 (10) [23.8, 68.4]
Month 6	1,843.2 (161) [1,592.2, 2,133.8]	2,664.7 (40) [1,986.6, 3,574.3]	1,983.5 (201) [1,738.2, 2,263.5]	24.1 (48) [18.5, 31.5]
Month 12	2,158.2 (159) [1,846.6, 2,522.4]	2,264.4 (40) [1,659.4, 3,090.1]	2,179.2 (199) [1,896.2, 2,504.4]	24.8 (47) [18.6, 33.1]

The per-protocol population consists of all vaccinated participants with serology data who had a serum sample collected within an acceptable day range and did not violate inclusion/exclusion criteria.
N=number of participants with serology data at one or more timepoints according to the intervention to which they were randomized.
n=number of participants contributing to the analysis.
CI=confidence interval; GP-ELISA=anti-glycoprotein human enzyme-linked immunosorbent assay (EU/mL); GMT=geometric mean titer.
[a] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.
[b] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose.
[c] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose.



Cohort 1 Adults CD4>=500 1 dose at Day 28.
Cohort 2 Adults CD4 >350 and <500 1 dose at Day 28.
Cohort 3 Adults CD4 >=200 and <=350 1 dose at Day 28.
Cohort 4 Adolescents CD4>=200 1 dose at Day 28.

Figure 2: Reverse Cumulative Distribution Plot of GP-ELISA Titres by Timepoint (GP-ELISA Per-Protocol Immunogenicity Population – V920 1 Dose - Cohort 1 to Cohort 4)

In the CSR, GP-ELISA GMTs are presented separately by cohort and by subgroup (adults, adolescents, female, male, GP-ELISA baseline levels [≥200 EU/mL or <200 EU/mL], African sites participants, Canadian sites participants).

The number of subjects in these analyses is limited to conclude on differences across cohort/subgroups, following trends are however noted (not discussed by MAH):

1. For cohort 1 (adults with CD4 T cell counts ≥500 cells/mm3) there was no notable trend towards an increase in GMTs at Month 6 and Month 12 as compared to Day 28 GMT in the V920 1-dose (*Table 11*), while for cohort 2 (adults with CD4 T cell counts ranging from 350-500 cells/mm3) and for cohort 3 (adults with CD4 T cell counts ranging from ≥200 to ≤350 cells/mm3) increases in GMTs at Month 6 and Month 12 as compared to Day 28 GMT in the V920 1-dose group are marked (respectively Table 12 and Table 13).

   For all adults (Cohort 1, 2 and 3), GP-ELISA GMTs rose from 32.3 EU/mL (N=118) at baseline to 1,170.8 (N=121) at Month 1, 1,724.0 (N=121) at Month 6 and 1,942.7 (N=119) at Month 12.

Table 11: Summary of Geometric Mean Titres (GP-ELISA Per-Protocol Immunogenicity Population) (Cohort 1 Adults CD4⩾500, 1 Dose)

Assay Time Point	V920 (N=40) GMT (n) [95% CI]	Placebo (N=10) GMT (n) [95% CI]
GP-ELISA		
Baseline	27.2 (38) [18.0, 41.0]	18.1 (10) [8.1, 40.2]
Day 28	1,655.0 (40) [1,151.4, 2,378.9]	18.1 (10) [8.7, 37.3]
Month 6	1,442.9 (40) [1,020.6, 2,039.9]	18.1 (10) [9.0, 36.1]
Month 12	1,428.1 (39) [971.9, 2,098.3]	30.1 (9) [13.5, 67.0]

The per-protocol population consists of all vaccinated participants with serology data who had a serum sample collected within an acceptable day range and did not violate inclusion/exclusion criteria.
N=number of participants with serology data at one or more timepoints according to the intervention to which they were randomized.
n=number of participants contributing to the analysis.
CI=confidence interval; GP-ELISA=anti-glycoprotein human enzyme-linked immunosorbent assay (EU/mL); GMT=geometric mean titer.

Table 12: Summary of Geometric Mean Titres (GP-ELISA Per-Protocol Immunogenicity Population) (Cohort 2 Adults CD4 >350 and <500, 1 Dose)

Assay Time Point	V920 (N=40) GMT (n) [95% CI]	Placebo (N=10) GMT (n) [95% CI]
GP-ELISA		
Baseline	33.8 (39) [25.2, 45.5]	19.6 (10) [10.9, 35.2]
Day 28	1,124.6 (40) [821.0, 1,540.4]	26.8 (9) [13.8, 52.0]
Month 6	2,387.0 (40) [1,717.2, 3,318.2]	21.7 (9) [10.8, 43.4]
Month 12	2,755.0 (40) [2,004.9, 3,785.9]	20.5 (9) [10.5, 40.0]

The per-protocol population consists of all vaccinated participants with serology data who had a serum sample collected within an acceptable day range and did not violate inclusion/exclusion criteria.
N=number of participants with serology data at one or more timepoints according to the intervention to which they were randomized.
n=number of participants contributing to the analysis.
CI=confidence interval; GP-ELISA=anti-glycoprotein human enzyme-linked immunosorbent assay (EU/mL); GMT=geometric mean titer.

Table 13: Summary of Geometric Mean Titres (GP-ELISA Per-Protocol Immunogenicity Population) (Cohort 3 Adults CD4≥ 200 and ≤350, 1 Dose)

Assay Time Point	V920 (N=41) GMT (n) [95% CI]	Placebo (N=9) GMT (n) [95% CI]
GP-ELISA		
Baseline	36.2 (41) [26.5, 49.4]	32.4 (9) [16.7, 62.9]
Day 28	868.8 (41) [679.0, 1,111.6]	29.7 (9) [17.5, 50.2]
Month 6	1,493.1 (41) [1,102.7, 2,021.7]	22.7 (9) [11.9, 43.3]
Month 12	1,849.3 (40) [1,361.6, 2,511.7]	25.1 (9) [13.2, 47.9]

The per-protocol population consists of all vaccinated participants with serology data who had a serum sample collected within an acceptable day range and did not violate inclusion/exclusion criteria.
N=number of participants with serology data at one or more timepoints according to the intervention to which they were randomized.
n=number of participants contributing to the analysis.
CI=confidence interval; GP-ELISA=anti-glycoprotein human enzyme-linked immunosorbent assay (EU/mL); GMT=geometric mean titer.

2. Marked increase in GMTs at Month 12 as compared to Day 28 GMT in the V920 1-dose in cohort 4 (adolescents with CD4 T cell counts ≥200 cell/mm3), with Day 28 GMT of 1,432.8 EU/mL (95% CI: 1,091.0, 1,881.8 / n=40) and Month 12 GMT of 2,951.3 (95% CI: 2,142.2, 4,066.0 / n=40) as shown in Table 14.

Table 14: Summary of Geometric Mean Titres (GP-ELISA Per-Protocol Immunogenicity Population) (Cohort 4 Adolescents CD4≥200, 1 Dose)

Assay Time Point	V920 (N=40) GMT (n) [95% CI]	Placebo (N=10) GMT (n) [95% CI]
GP-ELISA		
Baseline	36.3 (40) [25.8, 51.0]	37.0 (10) [18.7, 73.3]
Day 28	1,432.8 (40) [1,091.0, 1,881.8]	30.4 (10) [17.6, 52.4]
Month 6	2,256.4 (40) [1,736.8, 2,931.3]	24.7 (10) [14.6, 41.6]
Month 12	2,951.3 (40) [2,142.2, 4,066.0]	25.1 (10) [13.2, 47.7]

The per-protocol population consists of all vaccinated participants with serology data who had a serum sample collected within an acceptable day range and did not violate inclusion/exclusion criteria.
N=number of participants with serology data at one or more timepoints according to the intervention to which they were randomized.
n=number of participants contributing to the analysis.
CI=confidence interval; GP-ELISA=anti-glycoprotein human enzyme-linked immunosorbent assay (EU/mL); GMT=geometric mean titer.

3. Trends towards higher GMTs estimated in adolescents as compared to adults, which is consistent with data from the PREVAC study.

4. Trends towards higher GMTs estimated in female participants as compared to male participants, which is consistent with data from the PREVAC study.

5. When comparing GMTs measured after 1 dose of V920 from participants recruited in African sites (Table 15) with GMTs measured after 1 dose of V920 from participants recruited in Canadian sites (Table 16) it is noted that:

    a. Day 28 GMTs were comparatively higher in Canadian sites participants (2,058.4 EU/ml [95% CI: 1,367.2, 3,099.2] for n=20 subjects) as compared to African sites participants (1,144.5 EU/ml [95% CI: 973.4, 1,345.6] for n=141 subjects). At Canadian sites 20/21 participants who were administered V920 were from cohort 1 (adults with CD4 T cell counts ≥500 cells/mm3) and only 1 was from cohort 2.

    b. Marked increase in GMTs at Month 12 as compared to Day 28 GMT in the V920 1-dose in participants recruited from African sites, with Day 28 GMT of 1,144.5 EU/mL [95% CI:

973.4, 1,345.6], n=141) and Month 12 GMT of 2,280.2 EU/mL [95% CI: 1,929.9, 2,694.2], n=140) as shown in Table 15; while GMTs in participants recruited from Canadian sites decrease between Day 28 and Month 12 after 1-dose V920 (Table 16: Day 28 GMT of 2,058.4 EU/ml [95% CI: 1,367.2, 3,099.2] for n=20 subjects and Month 12 GMT of 1,439.1 EU/ml [95% CI: 932.1, 2,222.0] for n=19 subjects).

Table 15: Summary of Geometric Mean Titers (GP-ELISA Per-Protocol Immunogenicity Population) (Cohort 1 to Cohort 5) (Burkina Faso and Senegal)

Assay Time Point	V920 1 Dose[a] (N=141) GMT (n) [95% CI]	V920 2 Dose[b] (N=40) GMT (n) [95% CI]	Pooled V920[c] (N=181) GMT (n) [95% CI]	Placebo[c] (N=44) GMT (n) [95% CI]
GP-ELISA				
Baseline	35.1 (140) [29.2, 42.2]	40.6 (40) [28.8, 57.2]	36.3 (180) [30.9, 42.6]	29.8 (44) [21.5, 41.3]
Day 28	1,144.5 (141) [973.4, 1,345.6]	1,191.8 (40) [879.4, 1,615.1]	1,154.8 (181) [1,001.3, 1,331.8]	30.1 (43) [22.4, 40.3]
Day 56[b]		1,469.0 (40) [1,122.3, 1,923.0]	1,469.0 (40) [1,122.3, 1,923.0]	32.8 (10) [19.2, 56.3]
Day 84[b]		8,416.0 (40) [6,461.9, 10,961.1]	8,416.0 (40) [6,461.9, 10,961.1]	40.3 (10) [23.8, 68.4]
Month 6	1,876.9 (141) [1,600.2, 2,201.4]	2,664.7 (40) [1,975.2, 3,594.9]	2,028.0 (181) [1,760.0, 2,336.9]	25.0 (43) [18.7, 33.3]
Month 12	2,280.2 (140) [1,929.9, 2,694.2]	2,264.4 (40) [1,657.3, 3,093.9]	2,276.7 (180) [1,965.9, 2,636.7]	25.6 (43) [18.9, 34.6]

The per-protocol population consists of all vaccinated participants with serology data who had a serum sample collected within an acceptable day range and did not violate inclusion/exclusion criteria.
N=number of participants with serology data at one or more timepoints according to the intervention to which they were randomized.
n=number of participants contributing to the analysis.
CI=confidence interval; GP-ELISA=anti-glycoprotein human enzyme-linked immunosorbent assay (EU/mL); GMT=geometric mean titer.
[a] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.
[b] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose.
[c] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose.

Table 16: Summary of Geometric Mean Titers (GP-ELISA Per-Protocol Immunogenicity Population) (Cohort 1 to Cohort 5) (Canada)

Assay Time Point	V920 1 Dose[a] (N=20) GMT (n) [95% CI]	Pooled V920[c] (N=20) GMT (n) [95% CI]	Placebo[c] (N=5) GMT (n) [95% CI]
GP-ELISA			
Baseline	21.7 (18) [17.0, 27.7]	21.7 (18) [17.0, 27.7]	18.1 (5) [11.4, 28.7]
Day 28	2,058.4 (20) [1,367.2, 3,099.2]	2,058.4 (20) [1,367.2, 3,099.2]	18.1 (5) [8.0, 40.9]
Month 6	1,622.5 (20) [1,133.2, 2,323.1]	1,622.5 (20) [1,133.2, 2,323.1]	18.1 (5) [8.8, 37.0]
Month 12	1,439.1 (19) [932.1, 2,222.0]	1,439.1 (19) [932.1, 2,222.0]	18.1 (4) [7.0, 46.5]

The per-protocol population consists of all vaccinated participants with serology data who had a serum sample collected within an acceptable day range and did not violate inclusion/exclusion criteria.
N=number of participants with serology data at one or more timepoints according to the intervention to which they were randomized.
n=number of participants contributing to the analysis.
CI=confidence interval; GP-ELISA=anti-glycoprotein human enzyme-linked immunosorbent assay (EU/mL); GMT=geometric mean titer.
[a] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.
[b] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose.
[c] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose.

Summary of GP-ELISA Geometric Mean Fold Increase

As shown in Table 17, relatively to GP-ELISA GMFI, the following is noted:

- For the 1-dose V920 group (Cohorts 1 to 4 combined), GP-ELISA titres increased by 36.7-fold (95% CI: 30.4-44.2 / n=158) from baseline to Day 28 and remained elevated with trends towards increases in GMFIs at Month 6 (GMFI 55.5 [95% CI: 45.3, 67.9] for n=158) and at Month 12 (GMFI 64.5 [95% CI: 52.4, 79.5] for n=157) as compared to baseline.

- For the 2-dose V920 group (Cohort 5), GP-ELISA titres from baseline peaked at Day 84 (approximately 207-fold). The GMFIs for the 2-dose V920 group were generally comparable with the 1-dose V920 group (Cohorts 1 to 4 combined) at Months 6 and 12.
- No fold increase in GP-ELISA titres was observed at any timepoint in the pooled placebo group (Cohorts 1 to 5 combined).

Table 17: Summary of Geometric Mean Fold Increase (GP-ELISA Per-Protocol Immunogenicity Population - Cohort 1 to Cohort 5)

Assay Time Point	V920 1 Dose[a] (N=161) GMFI (n) [95% CI]	V920 2 Dose[b] (N=40) GMFI (n) [95% CI]	Pooled V920[c] (N=201) GMFI (n) [95% CI]	Placebo[c] (N=49) GMFI (n) [95% CI]
GP-ELISA				
Day 28	36.7 (158) [30.4, 44.2]	29.4 (40) [20.3, 42.5]	35.1 (198) [29.7, 41.4]	1.0 (48) [0.7, 1.4]
Day 56[b]		36.2 (40) [24.8, 52.9]	36.2 (40) [24.8, 52.9]	0.8 (10) [0.4, 1.6]
Day 84[b]		207.4 (40) [143.0, 300.6]	207.4 (40) [143.0, 300.6]	0.9 (10) [0.4, 2.0]
Month 6	55.5 (158) [45.3, 67.9]	65.7 (40) [44.0, 98.1]	57.4 (198) [47.9, 68.7]	0.8 (48) [0.6, 1.2]
Month 12	64.5 (157) [52.4, 79.5]	55.8 (40) [36.9, 84.4]	62.7 (197) [52.0, 75.5]	0.9 (47) [0.6, 1.3]

The per-protocol population consists of all vaccinated participants with serology data who had a serum sample collected within an acceptable day range and did not violate inclusion/exclusion criteria.

N=number of participants with serology data at one or more timepoints according to the intervention to which they were randomized.

n=number of participants contributing to the analysis. Participant must have serology data at baseline and timepoint.

GMFI=geometric mean fold increase; CI=confidence interval; GP-ELISA=anti-glycoprotein human enzyme-linked immunosorbent assay (EU/mL).

[a] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.

[b] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose.

[c] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose.

Summary of GP-ELISA Seroresponse Rates

Most (≥98%) participants in the pooled V920 group (Cohorts 1 to 5 combined) had a seroresponse (≥2-fold increase from baseline and ≥200 EU/mL, or ≥4-fold increase from baseline) at any time post-vaccination. Few (<11%) participants who received placebo had a seroresponse by either definition.

After Vaccination 2 in the 2-dose V920 group (Cohort 5), all participants had seroresponse by either definition at Day 84, which remained through Month 6. At Month 12, the proportions of participants in the 2-dose V920 group with a seroresponse by either definition were generally comparable with the proportion at Day 28 and with the 1-dose V920 group (Cohorts 1 to 4 combined) at Month 12.

Immunogenicity Results - PRNT

Summary of PRNT Geometric Mean Titers

The PRNT GMTs for the 1-dose V920 (Cohorts 1 to 4 combined) and the 2-dose V920 (Cohort 5) groups are shown in Table 18.

Data indicate that:

- GMTs increased post-vaccination and remained elevated through Month 12. Similarly to what observed for GP-ELISA GMTs, a trend towards increase in PRNT GMTs at Month 12 as compared to Day 28 GMT in the V920 1-dose group is noted.
- Post-vaccination GMTs were higher than those of the pooled placebo group at all timepoints after baseline.

- The PRNT GMTs of the 2-dose V920 group (Cohort 5) peaked at Day 84 and decreased at Months 6 and 12. The 2-dose V920 group had generally comparable concentrations as the 1-dose V920 group (Cohorts 1 to 4 combined) at Month 12.

Table 18: Summary of Geometric Mean Titers (PRNT Per-Protocol Immunogenicity Population - Cohort 1 to Cohort 5)

Assay Time Point	V920 1 Dose[a] (N=161) GMT (n) [95% CI]	V920 2 Dose[b] (N=40) GMT (n) [95% CI]	Pooled V920[c] (N=201) GMT (n) [95% CI]	Placebo[c] (N=49) GMT (n) [95% CI]
PRNT				
Baseline	17.7 (161) [17.4, 18.1]	17.5 (40) [16.7, 18.3]	17.7 (201) [17.4, 18.1]	17.5 (49) [16.8, 18.2]
Day 28	237.0 (161) [204.2, 275.0]	119.8 (40) [88.9, 161.5]	206.9 (201) [180.4, 237.3]	17.5 (48) [13.3, 23.0]
Day 56[b]		166.0 (40) [134.4, 205.1]	166.0 (40) [134.4, 205.1]	17.5 (10) [11.5, 26.7]
Day 84[b]		1,516.2 (40) [1,250.0, 1,838.9]	1,516.2 (40) [1,250.0, 1,838.9]	17.5 (10) [11.9, 25.7]
Month 6	250.2 (161) [217.8, 287.6]	415.1 (40) [314.0, 548.7]	276.8 (201) [243.8, 314.2]	17.5 (48) [13.6, 22.6]
Month 12	361.4 (159) [314.4, 415.3]	434.2 (40) [329.1, 573.0]	375.0 (199) [331.1, 424.6]	18.7 (47) [14.5, 24.1]

The per-protocol population consists of all vaccinated participants with serology data who had a serum sample collected within an acceptable day range and did not violate inclusion/exclusion criteria.

N=number of participants with serology data at one or more timepoints according to the intervention to which they were randomized.

n=number of participants contributing to the analysis.

CI=confidence interval; PRNT=plaque reduction neutralization test; GMT=geometric mean titer.

[a] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.

[b] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose.

[c] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose.

In the CSR, PRNT GMTs are presented separately by cohort and by subgroup (adults, adolescents, female, male, GP-ELISA baseline levels (≥200 EU/mL or <200 EU/mL), African sites participants, Canadian sites participants).

In adults PRNT GMTs increased from 17.8 (N=121) at baseline to 223.8 (N=121) at Month 1, 237.5 (N=121) at Month 6 and 338.0 (N=119) at Month 12. In adolescents PRNT GMTs rose from 17.5 (N=40) at baseline to 281.9 (N=40) at Month 1, 293.0 (N=40) at Month 6 and 440.9 (N=40) at Month 12.

The number of subjects in these analyses is limited to conclude on differences across cohort/subgroups, trends similar to those described in "Summary of GP-ELISA Geometric Mean Titres" are however noted.

Summary of PRNT Geometric Mean Fold Increase

As shown in Table 19, relatively to PRNT GMFI, the following is noted:

- For the 1-dose V920 group (Cohorts 1 to 4 combined), PRNT titres increased by 13.4-fold (95% CI: 11.5-15.5 / n=161) from baseline to Day 28 and remained elevated with trends towards increases in GMFIs at Month 12 (GMFI 20.4 [95% CI: 17.7, 23.5] for n=159) as compared to baseline.
- For the 2-dose V920 group (Cohort 5), PRNT titres from baseline peaked at Day 84 (86.6-fold). The GMFI for the 2-dose V920 group was generally comparable with the 1-dose V920 group (Cohorts 1 to 4 combined) at Month 12.
- No fold increase in PRNT titres was observed at any timepoint in the pooled placebo group (Cohorts 1 to 5 combined).

Table 19: Summary of Geometric Mean Fold Increase (PRNT Per-Protocol Immunogenicity Population - Cohort 1 to Cohort 5)

Assay Time Point	V920 1 Dose[a] (N=161) GMFI (n) [95% CI]	V920 2 Dose[b] (N=40) GMFI (n) [95% CI]	Pooled V920[c] (N=201) GMFI (n) [95% CI]	Placebo[c] (N=49) GMFI (n) [95% CI]
PRNT				
Day 28	13.4 (161) [11.5, 15.5]	6.8 (40) [5.0, 9.3]	11.7 (201) [10.2, 13.4]	1.0 (48) [0.8, 1.3]
Day 56[b]		9.5 (40) [7.7, 11.7]	9.5 (40) [7.7, 11.7]	1.0 (10) [0.7, 1.5]
Day 84[b]		86.6 (40) [71.4, 105.1]	86.6 (40) [71.4, 105.1]	1.0 (10) [0.7, 1.5]
Month 6	14.1 (161) [12.2, 16.3]	23.7 (40) [17.8, 31.5]	15.6 (201) [13.7, 17.8]	1.0 (48) [0.8, 1.3]
Month 12	20.4 (159) [17.7, 23.5]	24.8 (40) [18.7, 32.9]	21.2 (199) [18.7, 24.1]	1.1 (47) [0.8, 1.4]

The per-protocol population consists of all vaccinated participants with serology data who had a serum sample collected within an acceptable day range and did not violate inclusion/exclusion criteria.

N=number of participants with serology data at one or more timepoints according to the intervention to which they were randomized.

n=number of participants contributing to the analysis. Participant must have serology data at baseline and timepoint.

GMFI=geometric mean fold increase; CI=confidence interval; PRNT=plaque reduction neutralization test.

[a] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.

[b] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose.

[c] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose.

Summary of PRNT Seroresponse Rates

Most (98.0%) participants in the pooled V920 group (Cohorts 1 to 5 combined) had a seroresponse defined as ≥4-fold increase from baseline at any time post-vaccination (Table 14.2-87). Few (2.1%) participants who received placebo had a seroresponse by this definition.

After Vaccination 2 in the 2-dose V920 group (Cohort 5), all participants had a seroresponse defined as ≥4-fold increase from baseline at Day 84, which remained elevated through Month 12.

6.3. Discussion

V920-015 is a Phase 2 Randomized, Multi-Center Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Immunogenicity of 1 or 2 doses of the V920 (rVSVΔG-ZEBOV-GP) Ebola Virus Vaccine Candidate in adolescents and adults 13 to 70 years of age (inclusive) living with HIV.

Study V920-015 has been conducted in Canada, Burkina Faso and Senegal (non-endemic for EBOV) from November 2017 (first participant first visit 01/11/2017) to March 2023 (last participant last visit 03/03/2023).

Methods

The overall trial design (including its amendments) is deemed acceptable.

Briefly, the study was designed to enrol sequentially 5 study cohorts based on CD4+ T cell counts and age, with 50 participants planned to be enrolled per cohort to be randomly assigned to receive 1 dose of V920 or placebo in a 4:1 ratio. In Cohort 5, adolescent and adult participants were to be randomly assigned to receive 1 dose of V920 or placebo in a 4:1 ratio on Day 0, followed by booster vaccination at Day 56 (matching vaccine).

The intended study populations were non-pregnant adolescents and adults living with HIV on antiretroviral therapy with undetectable HIV loads and CD4+ T cell counts above 200 cell/mm3, which is deemed appropriate to study safety and immunogenicity of ERVEBO in PLwHIV that have a controlled HIV infection and are not immunocompromised based on CD4+ T cell counts. In addition, participants with

history of infection with a filovirus or VSV and that had participated in a filovirus vaccine study or received a VSV-vectored vaccine were excluded.

The primary immunogenicity objectives of the MAH were to demonstrate that in adolescent and adult living with HIV (Cohorts 1 to 5 combined) V920 is superior to placebo for the antibody response (GP-ELISA GMT) on Day 28 (after administration of 1 dose) and for Cohort 5 on Day 84 (equivalent to 28 days after administration of the second dose of vaccine). Secondary immunogenicity objectives included descriptive analyses of the humoral immune responses (determined by GP-ELISA and PRNT assays) at different time-points through 1-year post-vaccination. Descriptive immunogenicity results (GMTs, GMFIs, seroresponse) were provided overall and by subgroup to explore the impact of CD4+ T cell counts, age, sex, baseline GP-ELISA, country (Africa and ex-Africa) on immunogenicity results.

Objectives and endpoints related to clinical immune responses are endorsed. Applied methodologies to assess post-vaccination immune responses (GP-ELISA and rVSVΔG -ZEBOV-GP PRNT) and applied definitions of seroresponse appear aligned with those of previous clinical studies from MAA and EoI (EMEA/H/C/004554/II/0025).

In study V920-015, 3 different V920 Drug Product Lots were used, all had a potency ≥2 x 10E7 pfu/mL. Data on distribution by cohort/country were not provided. This is a limitation given the differences in potency of the different lots, ranging from 5.4 x 10E7 pfu/mL to 3.0 x 10E8 pfu/mL.

Results

In total, 251 participants were randomized and a total of 250 participants in Cohorts 1 to 5 were vaccinated (201 in the pooled V920 group, 49 in the pooled placebo group) and included in the immunogenicity and safety populations.

Overall demographic characteristics (combined cohorts) show that the majority of participants had a baseline GP-ELISA <200 EU/mL (91.6%). There were 52.2% participants with a CD4+ T cell count ≥500 cells/mm3 (remaining participants were evenly distributed among participants with CD4 T cell counts 350-500 cells/mm3 and participants with CD4 T cell counts ≥200 to ≤350 cells/mm3). Age ranges were comparable between arms, with 25.9% adolescent participants and most recruited adults aged 18-49 years (55% of total recruited adults) and only approximately 10% of recruited adults aged ≥60 years. Similar proportions of male and female were recruitment, with some imbalance between arms (higher proportion of V920 vaccinated male participants compared to placebo and lower proportion of V920 vaccinated female participants compared with placebo). Notably, the majority of the participants were randomized at the site in Burkina Faso (152/251; 60.6%), 73/251 (29.1%) were randomized at the site in Senegal and 26/251 (10.4%) in Canada. This is different from what originally planned per protocol (i.e. ~100 subjects from Canadian sites and of ~150 subjects from African sites planned per protocol). Based on the demographic characteristics described per cohort, 25/26 participants recruited in Canada were randomized in Cohort 1 (20/25 vaccinated with V920) and only 1/26 was randomized in Cohort 2 and V920 vaccinated. No adults were randomized for Cohort 3 and 5 and no adolescents were randomized for Cohort 4 and 5 in Canadian sites.

When considering the characteristics of participants of cohort 4 (Adolescents CD4+ T cell counts ≥200 cells/mm3, 1 Dose) and of cohort 5 (Adults and Adolescents CD4+ T cell counts ≥200 cells/mm3, 2 Dose), it is noted that the majority had a CD4 T cell counts ≥500 cells/mm3 (43/50 (86%) in cohort 4 and 37/50 (74%) in cohort 5).

Immune responses after 1 dose of V920

The GP-ELISA and PRNT results obtained within study V920-015 and expressed in GMTs, GMFIs, seroresponse rates (different definitions) collectively show that administration of a single dose of V920 results in sustained binding and neutralizing antibody responses up to Month 12 in adolescents and adults living with HIV on antiretroviral therapy with undetectable HIV loads and CD4+ T cell counts above 200 cell/mm3.

In Cohorts 1 to 5 combined, Day 28 GP-ELISA GMTs were significantly superior as compared to levels detected in placebo-administered participants. GP-ELISA and PRNT GMTs remained elevated and higher than those of the pooled placebo group through Month 12 after a single dose of V920.

An unexpected trend of an increase in GP-ELISA GMTs at Month 6 and Month 12 as compared to Day 28 GMT in the combined 1-dose cohorts is noted (also reflected in terms of GP-ELISA GMFIs results). Similarly, a trend towards an increase in PRNT GMT at Month 12 as compared to Day 28 GMT after 1 dose of V920 is noted (also reflected in terms of PRNT GMFIs results).

Indeed, based on the GP-ELISA GMTs data submitted:

- Stratified by cohort, it appears that for cohort 1 (adults with CD4 T cell counts ≥500 cells/mm3) there was no notable trend towards an increase in GMTs at Month 6 and Month 12 as compared to Day 28 GMT in the V920 1-dose, while for cohort 2 (adults with CD4 T cell counts ranging from 350-500 cells/mm3) and for cohort 3 (adults with CD4 T cell counts ranging from ≥200 to ≤350 cells/mm3) increases in GMTs at Month 6 and Month 12 as compared to Day 28 GMT in the V920 1-dose group are marked. In the adolescents of cohort 4, a marked increase in GMTs at Month 12 as compared to Day 28 GMT in the V920 is noted.
- Stratified by continent, it appears that Day 28 GMTs were comparatively higher for the V920 vaccinated participants of the Canadian sites versus participants of African sites; and that in vaccinated participants of African site there was a notable increase in GP-ELISA GMTs between Day 28 and Month 12, while GMTs decreased between Day 28 and Month 12 in vaccinated participants of Canadian sites.

Concerning the observed trend with increases over time in binding and neutralizing antibody responses, the MAH speculates that this might be related to the maturation of the immune response, which can result in a gradual increase or sustained elevation of antibody titres months after vaccination, even in the absence of additional antigen exposure. These unexpected trends in the evolution of antibody levels were also notable in other clinical studies, but they appear more pronounced in study V920-015. The MAH did not discuss whether differences in CD4+ T cell counts in the different cohorts and/or differences in recruitment country and/or differences in the administered lots (potency ranging from 5.4 x 10E7 pfu/mL to 3.0 x 10E8 pfu/mL) might have contributed to the observed increases over time of the measured binding and neutralizing antibody.

When comparing GP-ELISA GMTs in V920 vaccinated adolescents versus adults, a trend towards higher GMTs in adolescents is noted, which is consistent with data from the PREVAC V920-016 study discussed within the EoI type II variation procedure (EMEA/H/C/004554/II/0025).

Concerning humoral responses stratified by baseline GP-ELISA GMTs, only n=11 participants V920 vaccinated had a baseline GP-ELISA ≥200 EU/mL, analysis is therefore not possible. Concerning humoral responses stratified by sex, trends towards higher humoral responses in females are noted, this being consistent with stratified data from the PREVAC V920-016 study discussed within the EoI type II variation procedure (EMEA/H/C/004554/II/0025), although differences in immune responses between sex were less marked in study V920-015.

Immune responses after 2 doses of V920

In participants of cohort 5, administration of a 2nd dose of V920 eight weeks after the primary dose resulted in a boost of binding and neutralizing antibody responses at Day 84 (28 days after the second dose) and antibody levels gradually decreased to comparable concentrations as those measured for the 1-dose V920 group (Cohorts 1 to 4 combined) at Month 12. These results are consistent with data of the PREVAC V920-016 study discussed within the EoI type II variation procedure (EMEA/H/C/004554/II/0025). However, it is noted that GP-ELISA GMTs measured in Study 015 are comparatively higher than those measured in PREVAC following 2 doses of V920 (with same timing of 2nd dose administration and of sampling post dose 2).

Conclusion

V920 induces GP-specific binding and neutralizing antibody as observed at Day 28 post-vaccination in adolescent and adults living with a controlled HIV infection (defined as individuals on antiretroviral therapy with undetectable HIV loads and CD4+ T cell counts above 200 cell/mm3). At 1-year post-vaccination, Ab levels are still higher than pre-vaccination.

Administration of a second dose of V920 56 days after the primary dose results in a transient boost in binding and neutralizing antibody responses, which declined at Month 12 to levels comparable to those detected after a single primary dose. Need and appropriate timing of administration of a booster dose of V920 remains currently undetermined.

In the absence of ICP, the clinical relevance of those immunogenicity results is unknown.

7. Clinical Safety aspects

7.1. Methods – analysis of data submitted

Adolescents and adults 13 to 70 years of age (inclusive) living with HIV received either 1 or 2 doses of V920 or placebo and were followed for safety through 1 year after vaccination (1 year after first vaccination for those in the 2-dose group).

Table 20. Summary of Clinical Safety Study V920-015

Study Number (Status) [CTD Location] Number of Study Sites (Regions)	Design (Indication)	Number of Participants by Intervention Group	Study Population (N)	Primary Safety Endpoints
V920-015 (completed) [Ref. 5.3.5.1: P015V920] 4 centers in 3 countries (Canada, Burkina Faso, and Senegal)	Phase 2, randomized, double-blind, placebo-controlled, parallel-group study Adults and adolescents living with HIV who were 13 to 70 (inclusive) years of age Duration: 12 months postvaccination	Cohorts 1 to 4 (1 dose [Day 0]): V920 ≥2 x 10^7 pfu: 162 randomized, 161 vaccinated, 160 completed study, 1 discontinued study Placebo: 39 randomized, 39 vaccinated, 37 completed study, 2 discontinued study Cohort 5 (2 doses [Vaccination 1 on Day 0; Vaccination 2 on Day 56]): V920 ≥2 x 10^7 pfu (per dose): 40 randomized, vaccinated, and completed study Placebo: 10 randomized, vaccinated, and completed study	Cohorts 1 to 5: Sex: 121 Males/130 Females Overall median age (Range): 44 years (13 to 70 years)	• Solicited local and systemic AEs for 14 days after each vaccination • Fever, arthritis, arthralgia, rash, and blisters/vesicular lesions for 42 days after each vaccination • Unsolicited AEs for 42 days after each vaccination • Vaccine-related SAEs through to Day 365 • Changes in vital signs (eg, blood pressure, heart rate, respiratory rate, and temperature) • Changes in clinical laboratory values
AE=adverse event; CTD=common technical document; HIV=human immunodeficiency virus; N=number; pfu=plaque-forming unit; SAE=serious adverse event				

7.1.1. Overall Extent of Exposure

Safety analyses were based on the APaT population, which included randomized participants who received at least 1 dose of study intervention (V920 or placebo). A total of 250 participants in Cohorts 1 to 5 (201 in the pooled V920 group, 49 in the pooled placebo group) were included in the safety population as follows:

- 1 dose of V920 (Cohorts 1 to 4 combined): 161 participants
- 1 dose of placebo (Cohorts 1 to 4 combined): 39 participants
- 2 doses of V920 (Cohort 5): 40 participants
- 2 doses of placebo (Cohort 5): 10 participants

Details of the cohorts:

- Cohort 1 (CD4 ≥500 cells/mm3): 51 adults (41 vaccinated with V920, 10 with placebo)
- Cohort 2 (CD4 >350 to <500 cells/mm3): 50 adults (40 vaccinated with V920, 10 with placebo)
- Cohort 3 (CD4 ≥200 cells/mm3 and ≤350 cells/mm3): 50 adults (41 vaccinated with V920, 9 with placebo)
- Cohort 4 (CD4 ≥200 cells/mm3): 50 adolescents (40 vaccinated with V920, 10 with placebo)
- Cohort 5 (CD4 ≥200 cells/mm3): 35 adults (28 vaccinated with V920, 7 with placebo)
- Cohort 5 (CD4 ≥200 cells/mm3): 15 adolescents (12 vaccinated with V920, 3 with placebo)

7.1.2. Demographic and Other Characteristics of Study Population

The majority of the overall participants in all 5 cohorts were randomized at the site in Burkina Faso (60.6%) (Senegal: 29.1%, Canada: 10.4%), had a baseline GP-ELISA <200 EU/mL (91.6%), or had CD4 ≥500 cells/mm3 (52.2%). Demographic characteristics were generally comparable across study intervention groups (for age, race, BMI…). However, there was a higher proportion of male participants who received V920 (50.5%) compared with placebo (38.8%), and a lower proportion of females who received V920 (49.5%) compared with placebo (61.2%).

7.2. Results

Table 21. Adverse Event Summary (All Participants as Treated - Vaccination to 42 Days Postvaccination) (Cohort 1 to Cohort 5)

	V920 1 Dose[b]		V920 2 Dose[c]		Pooled V920[d]		Placebo[d]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population with follow-up	161		40		201		49	
with one or more adverse events	149	(92.5)	39	(97.5)	188	(93.5)	37	(75.5)
injection-site	105	(65.2)	30	(75.0)	135	(67.2)	14	(28.6)
non-injection-site	136	(84.5)	39	(97.5)	175	(87.1)	35	(71.4)
with no adverse event	12	(7.5)	1	(2.5)	13	(6.5)	12	(24.5)
with vaccine-related[a] adverse events	136	(84.5)	36	(90.0)	172	(85.6)	22	(44.9)
injection-site	105	(65.2)	30	(75.0)	135	(67.2)	14	(28.6)
non-injection-site	93	(57.8)	15	(37.5)	108	(53.7)	17	(34.7)
with serious adverse events	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
with serious vaccine-related[a] adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a vaccine-related[a] adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the vaccine.
[b] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.
[c] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose. For Cohort 5, adverse events are presented for 42 days postvaccination 1.
[d] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose. For Cohort 5, adverse events are presented for 42 days postvaccination 1.
MedDRA version 27.0 was used in the reporting of this study.

Table 22. Adverse Event Summary (All Participants as Treated – Second Vaccination to 42 Days Postvaccination 2) (Cohort 5 Adults and Adolescents CD4⩾200, 2 Dose)

	V920		Placebo	
	n	(%)	n	(%)
Participants in population with follow-up	40		10	
with one or more adverse events	29	(72.5)	7	(70.0)
injection-site	21	(52.5)	1	(10.0)
non-injection-site	22	(55.0)	7	(70.0)
with no adverse event	11	(27.5)	3	(30.0)
with vaccine-related[a] adverse events	24	(60.0)	6	(60.0)
injection-site	21	(52.5)	1	(10.0)
non-injection-site	8	(20.0)	5	(50.0)
with serious adverse events	0	(0.0)	1	(10.0)
with serious vaccine-related[a] adverse events	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)
who died due to a vaccine-related[a] adverse event	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the vaccine.
MedDRA version 27.0 was used in the reporting of this study.

Table 23. Adverse Event Summary (All Participants as Treated - Vaccination to 1 Year Postvaccination) (Cohort 1 to Cohort 5)

	V920 1 Dose[b]		V920 2 Dose[c]		Pooled V920[d]		Placebo[d]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population with follow-up	161		40		201		49	
with one or more adverse events	149	(92.5)	39	(97.5)	188	(93.5)	38	(77.6)
injection-site	105	(65.2)	30	(75.0)	135	(67.2)	14	(28.6)
non-injection-site	136	(84.5)	39	(97.5)	175	(87.1)	36	(73.5)
with no adverse event	12	(7.5)	1	(2.5)	13	(6.5)	11	(22.4)
with vaccine-related[a] adverse events	136	(84.5)	37	(92.5)	173	(86.1)	26	(53.1)
injection-site	105	(65.2)	30	(75.0)	135	(67.2)	14	(28.6)
non-injection-site	93	(57.8)	16	(40.0)	109	(54.2)	21	(42.9)
with serious adverse events	3	(1.9)	0	(0.0)	3	(1.5)	2	(4.1)
with serious vaccine-related[a] adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a vaccine-related[a] adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the vaccine.
[b] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.
[c] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose. For Cohort 5, adverse events are presented for 1 year postvaccination 1.
[d] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose. For Cohort 5, adverse events are presented for 1 year postvaccination 1.
MedDRA version 27.0 was used in the reporting of this study.

The majority of participants in the pooled V920 (93.5%) and pooled placebo (75.5%) groups (Cohorts 1 to 5 combined) experienced ≥1 AE within 42 days postvaccination (Vaccination 1 for Cohort 5) (Table 21). The proportions of participants who had injection-site AE (67.2%), systemic AE (87.1%), vaccine-related injection-site AE (67.2%), and vaccine-related systemic AE (53.7%) were higher in the pooled V920 group compared with the pooled placebo group (28.6%, 71.4%, 28.6%, and 34.7% respectively).

Overall, the proportions of participants who had AE within the 42-days postvaccination (after Vaccination 1 for Cohort 5) were generally slightly higher in the 2-dose group (cohort 5 after 1 vaccination) compared to the 1-dose V920 groups (cohorts 1 to 4) (Table 20).

In the 2-dose V920 group (cohort 5), the proportions of participants who had AE within 42-days after the 1st vaccination was higher than after the 2nd vaccination (Table 22).

The proportions of participants who had AE within 1-year postvaccination were similar to those within 42-days postvaccination (Table 23).

SAEs were reported for few participants within 1 year postvaccination (3 in the 1-dose V920 group and 2 in the placebo group) and none of the SAEs were considered to be related to study intervention by the investigator. No participant discontinued study intervention or the study due to an AE or died within 1 year postvaccination.

Per cohort, the proportions of participants who had an AE within the 42-days postvaccination were:

- Cohort 1 (adults): 97.5% in V920 group versus 80% in placebo;
- Cohort 2 (adults): 85% in V920 group versus 70% in placebo;
- Cohort 3 (adults): 92.7% in V920 group versus 66.7% in placebo;
- Cohort 4 (adolescents): 95% in V920 group versus 80% in placebo;
- Cohort 5 (adolescents + adults): 97.5% in V920 group versus 80% in placebo.

7.2.1. Common Adverse Events

7.2.1.1. Solicited Local and Systemic Adverse Events

Table 24. Participants With Solicited Adverse Events (Incidence > 0% in One or More Vaccination *Groups) (Local and Systemic) (All Participants as Treated – Vaccination to 14 Days Postvaccination) (Cohort 1 to Cohort 5)*

	V920 1 Dose[a]		V920 2 Dose[b]		Pooled V920[c]		Placebo[c]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population with follow-up	161		40		201		49	
with one or more solicited adverse events	142	(88.2)	35	(87.5)	177	(88.1)	30	(61.2)
with no solicited adverse events	19	(11.8)	5	(12.5)	24	(11.9)	19	(38.8)
Solicited local adverse event	**104**	**(64.6)**	**30**	**(75.0)**	**134**	**(66.7)**	**14**	**(28.6)**
Injection site erythema	9	(5.6)	0	(0.0)	9	(4.5)	2	(4.1)
Injection site pain	100	(62.1)	30	(75.0)	130	(64.7)	12	(24.5)
Injection site swelling	10	(6.2)	1	(2.5)	11	(5.5)	3	(6.1)
Solicited systemic adverse event	**119**	**(73.9)**	**32**	**(80.0)**	**151**	**(75.1)**	**26**	**(53.1)**
Abdominal pain	17	(10.6)	8	(20.0)	25	(12.4)	4	(8.2)
Arthralgia	40	(24.8)	10	(25.0)	50	(24.9)	4	(8.2)
Blister	2	(1.2)	0	(0.0)	2	(1.0)	0	(0.0)
Chills	27	(16.8)	6	(15.0)	33	(16.4)	2	(4.1)
Diarrhoea	15	(9.3)	2	(5.0)	17	(8.5)	3	(6.1)
Fatigue	71	(44.1)	20	(50.0)	91	(45.3)	11	(22.4)
Feeling hot	36	(22.4)	15	(37.5)	51	(25.4)	7	(14.3)
Headache	86	(53.4)	23	(57.5)	109	(54.2)	13	(26.5)
Hyperhidrosis	19	(11.8)	7	(17.5)	26	(12.9)	2	(4.1)
Joint swelling	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)
Myalgia	25	(15.5)	10	(25.0)	35	(17.4)	3	(6.1)
Nausea	19	(11.8)	9	(22.5)	28	(13.9)	3	(6.1)
Pyrexia	10	(6.2)	1	(2.5)	11	(5.5)	0	(0.0)
Rash	6	(3.7)	2	(5.0)	8	(4.0)	5	(10.2)

Every participant is counted a single time for each applicable row and column.
Pyrexia was defined as maximum temperature ≥100.4 °F (38.0 °C) solicited from vaccination to 14 days postvaccination.
[a] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.
[b] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose. For Cohort 5, adverse events are presented for 14 days postvaccination 1.
[c] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose. For Cohort 5, adverse events are presented for 14 days postvaccination 1.
MedDRA version 27.0 was used in the reporting of this study.

Table 25. Participants With Solicited Adverse Events (Incidence > 0% in One or More Vaccination Groups) (Local and Systemic) (All Participants as Treated - Second Vaccination to 14 Days Postvaccination 2) (Cohort 5 Adults and Adolescents CD4⩾200, 2 Dose)

	V920		Placebo	
	n	(%)	n	(%)
Participants in population with follow-up	40		10	
with one or more solicited adverse events	25	(62.5)	6	(60.0)
with no solicited adverse events	15	(37.5)	4	(40.0)
Solicited local adverse event	**21**	**(52.5)**	**1**	**(10.0)**
Injection site pain	20	(50.0)	1	(10.0)
Injection site swelling	1	(2.5)	0	(0.0)
Solicited systemic adverse event	**13**	**(32.5)**	**5**	**(50.0)**
Abdominal pain	4	(10.0)	1	(10.0)
Arthralgia	3	(7.5)	0	(0.0)
Blister	1	(2.5)	0	(0.0)
Chills	1	(2.5)	1	(10.0)
Diarrhoea	4	(10.0)	2	(20.0)
Fatigue	2	(5.0)	2	(20.0)
Feeling hot	3	(7.5)	1	(10.0)
Headache	6	(15.0)	1	(10.0)
Myalgia	0	(0.0)	2	(20.0)
Nausea	4	(10.0)	1	(10.0)
Pyrexia	1	(2.5)	0	(0.0)
Rash	1	(2.5)	0	(0.0)

Every participant is counted a single time for each applicable row and column.
Pyrexia was defined as maximum temperature ≥100.4 °F (38.0 °C) solicited from vaccination to 14 days postvaccination.
MedDRA version 27.0 was used in the reporting of this study.

The majority of participants in the pooled V920 (88.1%) and pooled placebo (61.2%) groups (Cohorts 1 to 5 combined) experienced ≥1 solicited AE within 14 days postvaccination (Vaccination 1 for Cohort 5) (Table 24). The proportions of participants who had solicited local AE (66.7%) and systemic AE (75.1%) were higher in the pooled V920 group compared with the pooled placebo group (28.6% and 53.1% respectively).

Overall, the proportions of participants who had solicited AE (for both local and systemic AE) within the 14 days postvaccination (after Vaccination 1 for Cohort 5) were generally slightly higher in the 2-dose group (cohort 5 after 1 vaccination) compared to the 1-dose V920 groups (cohorts 1 to 4) (Table 24).

In the 2-dose V920 group (cohort 5), the proportions of participants who had solicited AE within 14 days after the 1st vaccination was higher (87.5%) than within 14 days after the 2nd (62.5%) (Table 24 and Table 25).

In the pooled V920 group (Cohorts 1 to 5 combined), the reported solicited AEs within 14 days postvaccination (Vaccination 1 for Cohort 5) were (Table 24):

- Local: injection-site pain (64.7% versus 24.5% in placebo), swelling (5.5% vs. 6.1%, respectively), and erythema (4.5% vs. 4.1%)
- Systemic: headache (54.2% vs. 26.5% in placebo), fatigue (45.3% vs. 22.4%, respectively), feeling hot (25.4% vs. 14.3%), arthralgia (24.9% vs. 8.2%), myalgia (17.4% vs. 6.1%), chills (16.4% vs. 4.1%), nausea (13.9% vs. 6.1%), hyperhidrosis (12.9% vs. 4.1%), abdominal pain (12.4% vs. 8.2%), diarrhoea (8.5% vs. 6.1%), pyrexia (5.5% vs. 0%), rash (4% vs. 10.2%), and blister (1% vs. 0).

In the pooled V920 group, the majority of the solicited AE within 14 days postvaccination were mild (70.1%) or moderate (15.4%) in intensity. Six participants reported severe solicited AEs:

- 1-dose V920 group (5 participants): 3 chill, 3 fatigue, 2 feeling hot, 2 headache, 2 hyperhidrosis, 1 myalgia, 1 nausea, 2 pyrexia.

- 2-dose V920 group (1 participant after vaccination 1): 1 chill, 1 fatigue, 1 feeling hot, 1 headache, 1 hyperhidrosis, 1 myalgia.

Related events:

Table 26. Participants With Vaccine-Related Solicited Adverse Events (Incidence > 0% in One or More Vaccination Groups) (Local and Systemic) (All Participants as Treated – Vaccination to 14 Days Postvaccination) (Cohort 1 to Cohort 5)

	V920 1 Dose[a]		V920 2 Dose[b]		Pooled V920[c]		Placebo[c]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population with follow-up	161		40		201		49	
with one or more vaccine-related solicited adverse events	134	(83.2)	35	(87.5)	169	(84.1)	20	(40.8)
with no vaccine-related solicited adverse events	27	(16.8)	5	(12.5)	32	(15.9)	29	(59.2)
Solicited local adverse event	**104**	**(64.6)**	**30**	**(75.0)**	**134**	**(66.7)**	**14**	**(28.6)**
Injection site erythema	9	(5.6)	0	(0.0)	9	(4.5)	2	(4.1)
Injection site pain	100	(62.1)	30	(75.0)	130	(64.7)	12	(24.5)
Injection site swelling	10	(6.2)	1	(2.5)	11	(5.5)	3	(6.1)
Solicited systemic adverse event	**86**	**(53.4)**	**13**	**(32.5)**	**99**	**(49.3)**	**12**	**(24.5)**
Abdominal pain	9	(5.6)	5	(12.5)	14	(7.0)	1	(2.0)
Arthralgia	28	(17.4)	4	(10.0)	32	(15.9)	2	(4.1)
Blister	2	(1.2)	0	(0.0)	2	(1.0)	0	(0.0)
Chills	20	(12.4)	4	(10.0)	24	(11.9)	1	(2.0)
Diarrhoea	6	(3.7)	1	(2.5)	7	(3.5)	1	(2.0)
Fatigue	46	(28.6)	8	(20.0)	54	(26.9)	5	(10.2)
Feeling hot	18	(11.2)	7	(17.5)	25	(12.4)	3	(6.1)
Headache	47	(29.2)	8	(20.0)	55	(27.4)	5	(10.2)
Hyperhidrosis	10	(6.2)	5	(12.5)	15	(7.5)	2	(4.1)
Joint swelling	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)
Myalgia	15	(9.3)	5	(12.5)	20	(10.0)	1	(2.0)
Nausea	9	(5.6)	6	(15.0)	15	(7.5)	3	(6.1)
Pyrexia	10	(6.2)	1	(2.5)	11	(5.5)	0	(0.0)
Rash	2	(1.2)	2	(5.0)	4	(2.0)	1	(2.0)

Every participant is counted a single time for each applicable row and column.
Pyrexia was defined as maximum temperature ≥100.4 °F (38.0 °C) solicited from vaccination to 14 days postvaccination. All cases of pyrexia were determined by the investigator to be related.
[a] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.
[b] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose. For Cohort 5, adverse events are presented for 14 days postvaccination 1.
[c] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose. For Cohort 5, adverse events are presented for 14 days postvaccination 1.
MedDRA version 27.0 was used in the reporting of this study.

Up to 14 days after vaccination, all solicited local AE were assessed as related to the vaccine: 66.7% in the pooled V920 versus 28.6% in placebo (table above). The frequencies of the solicited systemic AE assessed as related to the vaccine were 49.3% in the pooled V920 (out of 75.1%) versus 24.5% in placebo (out of 53.1%).

In the 2-dose V920 group (cohort 5), the proportions of participants who had related solicited AE within 14 days after the 1st vaccination was higher (87.5%) than within 14 days after the 2nd (60%).

In the pooled V920 group (Cohorts 1 to 5 combined), the reported related solicited systemic AEs within 14 days postvaccination (Vaccination 1 for Cohort 5) were (table above): headache (27.4% vs. 10.2% in placebo), fatigue (26.9% vs. 10.2%, respectively), feeling hot (12.4% vs. 6.1%), arthralgia (15.9% vs. 4.1%), myalgia (10% vs. 2%), chills (11.9% vs. 2%), nausea (7.5% vs. 6.1%), hyperhidrosis (7.5% vs. 4.1%), abdominal pain (7% vs. 2%), diarrhoea (3.5% vs. 2%), pyrexia (5.5% vs. 0%), rash (2% vs. 2%), and blister (1% vs. 0). (Of note, all events of pyrexia were assessed as related to the vaccine.)

7.2.1.2. Solicited Events Specific to Postvaccination

Table 27. Participants With Solicited Adverse Events (Incidence > 0% in One or More Vaccination Groups) (Events *Specific to Postvaccination) (All Participants as Treated - Vaccination to 42 Days Postvaccination) (Cohort 1 to Cohort 5)*

	V920 1 Dose[a]		V920 2 Dose[b]		Pooled V920[c]		Placebo[c]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population with follow-up	161		40		201		49	
with one or more solicited adverse events	57	(35.4)	16	(40.0)	73	(36.3)	11	(22.4)
with no solicited adverse events	104	(64.6)	24	(60.0)	128	(63.7)	38	(77.6)
Solicited systemic adverse event	**57**	**(35.4)**	**16**	**(40.0)**	**73**	**(36.3)**	**11**	**(22.4)**
Arthralgia	46	(28.6)	12	(30.0)	58	(28.9)	8	(16.3)
Blister	3	(1.9)	0	(0.0)	3	(1.5)	0	(0.0)
Joint swelling	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)
Pyrexia	18	(11.2)	3	(7.5)	21	(10.4)	0	(0.0)
Rash	9	(5.6)	3	(7.5)	12	(6.0)	5	(10.2)

Every participant is counted a single time for each applicable row and column.
Pyrexia was defined as maximum temperature ≥100.4 °F (38.0 °C) solicited from vaccination to 42 days postvaccination.
[a] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.
[b] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose. For Cohort 5, adverse events are presented for 42 days postvaccination 1.
[c] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose. For Cohort 5, adverse events are presented for 42 days postvaccination 1.
MedDRA version 27.0 was used in the reporting of this study.

Table 28. Participants With Solicited Adverse Events (Incidence > 0% in One or More Vaccination Groups) (Events Specific to Postvaccination) (All Participants as Treated - Second Vaccination to 42 Days Postvaccination 2) (Cohort 5 Adults and Adolescents CD4⩾200, 2 Dose)

	V920		Placebo	
	n	(%)	n	(%)
Participants in population with follow-up	40		10	
with one or more solicited adverse events	8	(20.0)	2	(20.0)
with no solicited adverse events	32	(80.0)	8	(80.0)
Solicited systemic adverse event	**8**	**(20.0)**	**2**	**(20.0)**
Arthralgia	3	(7.5)	1	(10.0)
Blister	1	(2.5)	0	(0.0)
Pyrexia	1	(2.5)	0	(0.0)
Rash	3	(7.5)	1	(10.0)

Every participant is counted a single time for each applicable row and column.
Pyrexia was defined as maximum temperature ≥100.4 °F (38.0 °C) solicited from vaccination to 42 days postvaccination.
MedDRA version 27.0 was used in the reporting of this study.

Protocol-specified events collected postvaccination ("events specific to postvaccination") included joint pain, swelling or stiffness (arthralgia/arthritis) symptoms, rash, small vesicles and/or pyrexia reported from day of vaccination until Day 42 after vaccination (after each vaccination for Cohort 5).

The proportion of participants who had ≥1 solicited events specific to postvaccination within 42 days after vaccination (Vaccination 1 for Cohort 5) were higher in the pooled V920 group (36.3%) compared with the pooled placebo group (22.4%) (Table 27).

Overall, the proportions of participants who had solicited events specific to postvaccination within 42 days after vaccination (Vaccination 1 for Cohort 5) were slightly higher in the 2-dose group (cohort 5 after 1 vaccination) (40%) compared to the 1-dose V920 groups (cohorts 1 to 4) (35.4%) (Table 27).

In the 2-dose V920 group (cohort 5), the proportions of participants who had solicited events specific to postvaccination within 42 days after the 1st vaccination (40%) was higher than after the 2nd vaccination (20%).

In the pooled V920 group (Cohorts 1 to 5 combined), the reported solicited events specific to postvaccination within 42 days after vaccination (Vaccination 1 for Cohort 5) were: arthralgia (28.9% vs.

16.3% in placebo), pyrexia (10.4% vs. 0%, respectively), rash (6% vs. 10.2%, respectively), and blister (1.5% vs. 0, respectively) (Table 27).

In the pooled V920 group (Cohorts 1 to 5 combined), the frequencies of the reported solicited events specific to postvaccination within 42 days after vaccination are, overall, slightly higher than the frequencies observed 14 days after vaccination: arthralgia (24.9% vs. 8.2% in placebo), pyrexia (5.5% vs. 0%, respectively), rash (4% vs. 10.2%, respectively), and blister (1% vs. 0, respectively).

In the pooled V920 group, the majority of the solicited events specific to postvaccination within 42 days after vaccination were mild (29.4%) or moderate (7.5%) in intensity. Two participants reported severe solicited AEs in the 1-dose V920 group: 2 pyrexia.

Related events:

Table 29. Participants With Vaccine-Related Solicited Adverse Events (Incidence > 0% in One or More Vaccination Groups) (Events Specific to Postvaccination) (All Participants as Treated - Vaccination to 42 Days Postvaccination) (Cohort 1 to Cohort 5)

	V920 1 Dose[a]		V920 2 Dose[b]		Pooled V920[c]		Placebo[c]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population with follow-up	161		40		201		49	
with one or more vaccine-related solicited adverse events	48	(29.8)	9	(22.5)	57	(28.4)	5	(10.2)
with no vaccine-related solicited adverse events	113	(70.2)	31	(77.5)	144	(71.6)	44	(89.8)
Solicited systemic adverse event	**48**	**(29.8)**	**9**	**(22.5)**	**57**	**(28.4)**	**5**	**(10.2)**
Arthralgia	30	(18.6)	6	(15.0)	36	(17.9)	5	(10.2)
Blister	3	(1.9)	0	(0.0)	3	(1.5)	0	(0.0)
Joint swelling	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)
Pyrexia	18	(11.2)	3	(7.5)	21	(10.4)	0	(0.0)
Rash	4	(2.5)	2	(5.0)	6	(3.0)	1	(2.0)

Every participant is counted a single time for each applicable row and column.
Pyrexia was defined as maximum temperature ≥100.4 °F (38.0 °C) solicited from vaccination to 42 days postvaccination. All cases of pyrexia were determined by the investigator to be related.
[a] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.
[b] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose. For Cohort 5, adverse events are presented for 42 days postvaccination 1.
[c] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose. For Cohort 5, adverse events are presented for 42 days postvaccination 1.
MedDRA version 27.0 was used in the reporting of this study.

Most of the events specific to postvaccination within 42 days after vaccination (Vaccination 1 for Cohort 5) were assessed as related to the vaccine in the pooled V920 (28.4% out of 36.3%) and in placebo (10.2% out of 22.4%) (Table 29).

In the 2-dose V920 group (cohort 5), the proportions of participants who had related solicited events specific to postvaccination within 42 days after the 1st vaccination (22.5%) was slightly higher than after the 2nd vaccination (17.5%).

In the pooled V920 group (Cohorts 1 to 5 combined), the reported related solicited events specific to postvaccination within 42 days after vaccination (Vaccination 1 for Cohort 5) were: arthralgia (17.9% vs. 10.2% in placebo), pyrexia (10.4% vs. 0%, respectively), rash (3% vs. 2%, respectively), and blister (1.5% vs. 0, respectively) (Table 29).

In the pooled V920 group (Cohorts 1 to 5 combined), the frequencies of the reported related solicited events specific to postvaccination within 42 days after vaccination (table above) are slightly higher than the frequencies observed 14 days after vaccination (Table 26): arthralgia (15.9% vs. 4.1% in placebo), pyrexia (5.5% vs. 0%, respectively), rash (2% vs. 2%, respectively), and blister (1% vs. 0, respectively).

7.2.1.3. Unsolicited Adverse Events

Table 30. Participants With Unsolicited Adverse Events (Incidence > 0% in One or More Vaccination Groups) (All Participants as Treated - Vaccination to 42 Days Postvaccination) (Cohort 1 to Cohort 5)

	V920 1 Dose[a]		V920 2 Dose[b]		Pooled V920[c]		Placebo[c]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population with follow-up	161		40		201		49	
with one or more unsolicited adverse events	87	(54.0)	18	(45.0)	105	(52.2)	22	(44.9)
with no unsolicited adverse events	74	(46.0)	22	(55.0)	96	(47.8)	27	(55.1)
Blood and lymphatic system disorders	**1**	**(0.6)**	**0**	**(0.0)**	**1**	**(0.5)**	**0**	**(0.0)**
Lymphadenopathy	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Cardiac disorders	**1**	**(0.6)**	**0**	**(0.0)**	**1**	**(0.5)**	**0**	**(0.0)**
Angina pectoris	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Ear and labyrinth disorders	**1**	**(0.6)**	**0**	**(0.0)**	**1**	**(0.5)**	**0**	**(0.0)**
Cerumen impaction	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Eye disorders	**5**	**(3.1)**	**0**	**(0.0)**	**5**	**(2.5)**	**0**	**(0.0)**
Conjunctivitis allergic	3	(1.9)	0	(0.0)	3	(1.5)	0	(0.0)
Eye irritation	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Eye pain	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Gastrointestinal disorders	**18**	**(11.2)**	**4**	**(10.0)**	**22**	**(10.9)**	**3**	**(6.1)**
Abdominal pain	2	(1.2)	1	(2.5)	3	(1.5)	1	(2.0)
Abdominal pain upper	1	(0.6)	1	(2.5)	2	(1.0)	0	(0.0)
Dental caries	3	(1.9)	1	(2.5)	4	(2.0)	1	(2.0)
Diarrhoea	5	(3.1)	0	(0.0)	5	(2.5)	1	(2.0)
Dyspepsia	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Gastroduodenal ulcer	2	(1.2)	0	(0.0)	2	(1.0)	0	(0.0)
Gastrointestinal disorder	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Malpositioned teeth	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Oral papule	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Peptic ulcer	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Toothache	4	(2.5)	1	(2.5)	5	(2.5)	0	(0.0)
General disorders and administration site conditions	**15**	**(9.3)**	**0**	**(0.0)**	**15**	**(7.5)**	**3**	**(6.1)**
Chest pain	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Fatigue	8	(5.0)	0	(0.0)	8	(4.0)	2	(4.1)
Ill-defined disorder	2	(1.2)	0	(0.0)	2	(1.0)	0	(0.0)
Injection site induration	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Pain	4	(2.5)	0	(0.0)	4	(2.0)	1	(2.0)
Tenderness	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Infections and infestations	**50**	**(31.1)**	**7**	**(17.5)**	**57**	**(28.4)**	**13**	**(26.5)**
Amoebic dysentery	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)
Bronchitis	5	(3.1)	1	(2.5)	6	(3.0)	3	(6.1)
Conjunctivitis	3	(1.9)	1	(2.5)	4	(2.0)	2	(4.1)
Conjunctivitis bacterial	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Cutaneous leishmaniasis	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)
Cystitis	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Furuncle	2	(1.2)	0	(0.0)	2	(1.0)	1	(2.0)
Gastroenteritis	2	(1.2)	0	(0.0)	2	(1.0)	1	(2.0)
Influenza	1	(0.6)	0	(0.0)	1	(0.5)	2	(4.1)
Malaria	11	(6.8)	2	(5.0)	13	(6.5)	2	(4.1)
Nasopharyngitis	3	(1.9)	0	(0.0)	3	(1.5)	1	(2.0)
Orchitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)
Otitis media chronic	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)
Parasitic gastroenteritis	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Paronychia	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)

Pilonidal disease	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Pneumonia	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Rhinitis	9	(5.6)	3	(7.5)	12	(6.0)	1	(2.0)
Sinobronchitis	8	(5.0)	1	(2.5)	9	(4.5)	1	(2.0)
Tinea pedis	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Tonsillitis	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Tooth abscess	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Tooth infection	2	(1.2)	0	(0.0)	2	(1.0)	0	(0.0)
Typhoid fever	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Upper respiratory tract infection	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Urinary tract infection	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Vulvovaginal mycotic infection	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Injury, poisoning and procedural complications	**3**	**(1.9)**	**2**	**(5.0)**	**5**	**(2.5)**	**0**	**(0.0)**
Ankle fracture	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Limb injury	1	(0.6)	2	(5.0)	3	(1.5)	0	(0.0)
Thermal burn	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Metabolism and nutrition disorders	**3**	**(1.9)**	**0**	**(0.0)**	**3**	**(1.5)**	**0**	**(0.0)**
Decreased appetite	3	(1.9)	0	(0.0)	3	(1.5)	0	(0.0)
Musculoskeletal and connective tissue disorders	**3**	**(1.9)**	**1**	**(2.5)**	**4**	**(2.0)**	**2**	**(4.1)**
Back pain	1	(0.6)	0	(0.0)	1	(0.5)	1	(2.0)
Bursitis	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Myalgia	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)
Pain in extremity	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Torticollis	0	(0.0)	1	(2.5)	1	(0.5)	0	(0.0)
Nervous system disorders	**19**	**(11.8)**	**3**	**(7.5)**	**22**	**(10.9)**	**3**	**(6.1)**
Burning sensation	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Carpal tunnel syndrome	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Cervicobrachial syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)
Dizziness	8	(5.0)	0	(0.0)	8	(4.0)	1	(2.0)
Headache	7	(4.3)	3	(7.5)	10	(5.0)	1	(2.0)
Intercostal neuralgia	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Paraesthesia	2	(1.2)	0	(0.0)	2	(1.0)	0	(0.0)
Sciatica	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)
Psychiatric disorders	**3**	**(1.9)**	**0**	**(0.0)**	**3**	**(1.5)**	**0**	**(0.0)**
Insomnia	3	(1.9)	0	(0.0)	3	(1.5)	0	(0.0)
Reproductive system and breast disorders	**4**	**(2.5)**	**0**	**(0.0)**	**4**	**(2.0)**	**1**	**(2.0)**
Breast pain	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Dysmenorrhoea	1	(0.6)	0	(0.0)	1	(0.5)	1	(2.0)
Heavy menstrual bleeding	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Vaginal discharge	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**9**	**(5.6)**	**3**	**(7.5)**	**12**	**(6.0)**	**4**	**(8.2)**
Bronchopneumopathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)
Cough	7	(4.3)	3	(7.5)	10	(5.0)	3	(6.1)
Lung disorder	2	(1.2)	0	(0.0)	2	(1.0)	0	(0.0)
Oropharyngeal pain	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Skin and subcutaneous tissue disorders	**9**	**(5.6)**	**1**	**(2.5)**	**10**	**(5.0)**	**3**	**(6.1)**
Acne	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Ecchymosis	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Hyperhidrosis	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Intertrigo	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Prurigo	2	(1.2)	0	(0.0)	2	(1.0)	0	(0.0)
Pruritus	4	(2.5)	1	(2.5)	5	(2.5)	3	(6.1)
Vascular disorders	**2**	**(1.2)**	**1**	**(2.5)**	**3**	**(1.5)**	**1**	**(2.0)**
Diastolic hypertension	1	(0.6)	0	(0.0)	1	(0.5)	1	(2.0)
Hypertension	1	(0.6)	1	(2.5)	2	(1.0)	0	(0.0)

Every participant is counted a single time for each applicable row and column.

[a] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.

[b] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose. For Cohort 5, adverse events are presented for 42 days postvaccination 1.

[c] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose. For Cohort 5, adverse events are presented for 42 days postvaccination 1.

MedDRA version 27.0 was used in the reporting of this study.

Approximately half of the participants in the pooled V920 (52.2%) and pooled placebo (44.9%) groups (Cohorts 1 to 5 combined) had ≥1 unsolicited AE within 42 days postvaccination (Vaccination 1 for Cohort 5) (Table 28). The most frequently reported unsolicited AEs were in the following SOCs: infections and infestations (28.4 % in the pooled V920 versus 26.5% in the placebo), gastrointestinal disorders (10.9% vs. 6.1%, respectively), and nervous system disorders (10.9% vs. 6.1%, respectively). The proportions of participants who had unsolicited AEs was generally comparable between the pooled V920 and pooled placebo groups.

Overall, the proportions of participants who had unsolicited events within 42 days after vaccination (Vaccination 1 for Cohort 5) were slightly lower in the 2-dose group (cohort 5 after 1 vaccination) (45%) compared to the 1-dose V920 groups (cohorts 1 to 4) (54%) (Table 28).

In the 2-dose V920 group (cohort 5), the proportions of participants who had unsolicited events within 42 days after the 1st vaccination (45%) was slightly higher than after the 2nd vaccination (37.5%).

In the pooled V920 group, the majority of the unsolicited AE within the 42 days postvaccination were mild (43.3%) or moderate (10.4%) in intensity. Two participants reported severe solicited AEs in the 1-dose V920 group: 1 ankle fracture and 1 breast pain.

Related events:

Table 31. Participants With Vaccine-Related Unsolicited Adverse Events (Incidence > 0% in One or More Vaccination Groups) (All Participants as Treated - Vaccination to 42 Days Postvaccination) (Cohort 1 to Cohort 5)

	V920 1 Dose[a]		V920 2 Dose[b]		Pooled V920[c]		Placebo[c]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population with follow-up	161		40		201		49	
with one or more vaccine-related unsolicited adverse events	22	(13.7)	1	(2.5)	23	(11.4)	7	(14.3)
with no vaccine-related unsolicited adverse events	139	(86.3)	39	(97.5)	178	(88.6)	42	(85.7)
Blood and lymphatic system disorders	**1**	**(0.6)**	**0**	**(0.0)**	**1**	**(0.5)**	**0**	**(0.0)**
Lymphadenopathy	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Eye disorders	**1**	**(0.6)**	**0**	**(0.0)**	**1**	**(0.5)**	**0**	**(0.0)**
Conjunctivitis allergic	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Gastrointestinal disorders	**1**	**(0.6)**	**0**	**(0.0)**	**1**	**(0.5)**	**2**	**(4.1)**
Abdominal pain	1	(0.6)	0	(0.0)	1	(0.5)	1	(2.0)
Diarrhoea	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)
General disorders and administration site conditions	**8**	**(5.0)**	**0**	**(0.0)**	**8**	**(4.0)**	**1**	**(2.0)**
Fatigue	3	(1.9)	0	(0.0)	3	(1.5)	0	(0.0)
Ill-defined disorder	2	(1.2)	0	(0.0)	2	(1.0)	0	(0.0)
Injection site induration	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Pain	3	(1.9)	0	(0.0)	3	(1.5)	1	(2.0)
Infections and infestations	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.0)**
Influenza	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.0)**
Back pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)
Nervous system disorders	**7**	**(4.3)**	**1**	**(2.5)**	**8**	**(4.0)**	**1**	**(2.0)**
Dizziness	5	(3.1)	0	(0.0)	5	(2.5)	0	(0.0)
Headache	2	(1.2)	1	(2.5)	3	(1.5)	1	(2.0)
Skin and subcutaneous tissue disorders	**5**	**(3.1)**	**0**	**(0.0)**	**5**	**(2.5)**	**2**	**(4.1)**
Hyperhidrosis	1	(0.6)	0	(0.0)	1	(0.5)	0	(0.0)
Pruritus	4	(2.5)	0	(0.0)	4	(2.0)	2	(4.1)

Every participant is counted a single time for each applicable row and column.
[a] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.
[b] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose. For Cohort 5, adverse events are presented for 42 days postvaccination 1.
[c] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose. For Cohort 5, adverse events are presented for 42 days postvaccination 1.
MedDRA version 27.0 was used in the reporting of this study.

Within 42 days postvaccination, the frequencies of the unsolicited AE assessed as related to the vaccine were 11.4% in the pooled V920 (out of 52.2%) versus 14.3% in placebo (out of 44.9%) (table above). The most frequently reported related unsolicited AEs were in the following SOCs: nervous system disorders (4% vs. 2%, respectively) and the General disorders and administration site conditions SOC (4% vs. 2%, respectively). The most frequent related unsolicited AE in the pooled V920 were: dizziness (2.5% versus 0% in placebo), pruritus (2% vs. 4.1%, respectively), headache (1.5% vs. 2%, respectively), fatigue (1.5% vs. 0%, respectively), and pain (1.5% vs. 2%, respectively).

In the 2-dose V920 group (cohort 5), the proportions of participants who had related unsolicited events within 42 days after the 1st vaccination was the same than after the 2nd vaccination (2.5%).

7.2.2. Deaths

There were no reported deaths within 1-year postvaccination.

7.2.3. Other Serious Adverse Events

A total of 5 SAEs were reported within 1-year postvaccination (1 year after Vaccination 1 for Cohort 5) by 3 participants in the 1-dose V920 group: hepatitis toxic, erysipelas, malaria, ankle fracture, and thrombophlebitis. None of the SAEs were considered related to study intervention by the investigator.

One SAE of substance-induced psychotic disorder was reported 380 days postvaccination in the 1-dose V920 group. The SAE was severe in intensity and not considered related to study intervention by the investigator.

7.2.4. Discontinuations Due to Adverse Events

No participant discontinued study intervention or discontinued from the study due to an AE.

7.2.5. Clinical laboratory evaluations

Laboratory safety tests were collected at screening/baseline and Days 3, 7, 14, 28, 42, 56, 59, 63, 70, 84, and 98.

7.2.5.1. Laboratory Findings

Clinical laboratory analyses were to be performed to assess occurrence of any haematological (haemoglobin level, WBC, lymphocyte, neutrophil, eosinophil and platelet count) and biochemical (ALT, AST and creatinine) laboratory abnormality at days 0, 3, 7, 14, and 28 after each vaccination; decrease in CD4+ T cell-count (i.e., CD4+< 200 mm3); and increase in HIV viral load (i.e., VL > 50 c/ml over two consecutive measurements).

No clinically meaningful changes in chemistry or haematology, including CD4 counts, were observed for the overall population (Cohorts 1 to 5 combined), pooled adults, or pooled adolescents. The majority of the laboratory findings that met predetermined criteria were mild or moderate. Few participants had laboratory findings that were severe or potentially life-threatening.

7.2.5.2. Viremia and Shedding of V920 Over Time

Vaccine viraemia and shedding analyses included detection of rVSV by PCR in blood, urine, and saliva in all subjects. Samples were collected at Days 3, 7, 14, 28, and 42. Participants in the 2-dose groups (V920 and placebo) also had these samples collected at Days 56, 59, 63, 70, 84, and 98. Detection of rVSV by PCR in through 42 days from skin vesicles, joint fluid, or skin biopsies was also to be analysed if specimens were obtained. It is understood specimens were not obtained as no data were submitted.

Vaccine viraemia and shedding were assessed using a qualified Quantitative Real-time Reverse Transcription Polymerase Chain Reaction Assay (qRT-PCR) comparable to the one applied to assess viraemia and shedding in different trials (V920-009, -012, -016 and -018).

The VSVΔG-ZEBOV Quantitative Real-Time Reverse Transcription Polymerase Chain Reaction Assay (RT-PCR) is a real-time RT-PCR assay that targets RNA sequences at the junction of the vesicular stomatitis virus (VSV) and Ebola Zaire virus (ZEBOV) GP sequences in the vector such that this assay is specific for

the vaccine and does not detect wild-type VSV (Indiana or New Jersey) or ZEBOV. The assay is composed of three principal steps: (1) extraction of RNA from clinical specimens, (2) parallel amplification and detection of vector-specific sequences at the junction of the VSV matrix gene and the inserted ZEBOV GP gene and (3) quantification of the results of the real-time RT-PCR amplification. Quantification of RT-PCR results are calculated using an external standard curve of VSVΔG-ZEBOV GP calibrators and results are reported as copies/mL.

Results are presented based on the prespecified LLOD cutoffs, which were ≥7.8125 copies/mL in blood, ≥7.8125 copies/mL in urine, and ≥100 copies/mL in saliva.

Viraemia and vaccine shedding were analysed with counts, percentages, and exact 95% confidence intervals by vaccination group. Vaccine shedding and viremia were defined as rVSV RT-PCR ≥LLOD or rVSV RT-PCR>0. Results in terms of proportions of participants with viremia or shedding ≥LLOD and >0 are presented.

From Day 3 to Day 42 after vaccination (after Vaccination 1 for Cohort 5) in the pooled V920 group (Cohorts 1 to 5):

- The proportion of participants with detectable viremia or shedding decreased over time from Day 3 (79.6% of participants, 160/201) to Day 28 (1.5% of participants, 3/201), with no viremia or shedding >LLOD cutoffs or rVSV RT-PCR >0 detected at Day 42 in any participants administered V920 (Table 32).
- The proportion of participants with detectable viremia decreased over time from Day 3 (79.5% of participants, 159/200) to Day 28 (1.5% of participants, 3/198), with viremia >LLOD cutoff detected at Day 7 in 6/201 vaccinated subjects, and none at Days 14 and 42 (Table 33). This trend was observed in both adults and adolescents, with a higher proportion of adults (85.9%, 128/149) with detectable viremia at Day 3 as compared to adolescents (60.8%, 31/51). Maximum level of vaccine viraemia was detected at Day 3 (2,790 copies/mL for subject 3220) and in the 3 subjects that had detectable vaccine viraemia at Day 28, maximum level was 440 copies/mL (subject 4035).
- The proportion of participants shedding in saliva to levels ≥LLOD cutoff peaked at Day 7 (16.5% of participants, 33/200) and decreased at Day 14 (10.8% of participants, 21/195) (Table 34). Vaccine shedding in saliva > LLOD (100 copies/mL) was not detected at Days 28 and 42. This trend was observed in both adults and adolescents, with the proportions of participants generally comparable at each timepoint. Maximum level of vaccine shedding in saliva was detected at Day 7 (28,102 copies/mL for subject 4191). Maximum level detected at Day 3 was 13,828 (subject 4024) and maximum level detected at Day 14 was 3,223 (subject 4196).
- One participant (adult subject 3035) had shedding in urine ≥LLOD cutoff at Day 7, 76 copies/mL were detected in these participants. Vaccine shedding in urine was not detected at Days 28 and 42.

After the second vaccination in the 2-dose V920 group (Cohort 5):

- Three participants had detectable viremia ≥LLOD cutoff (Table 32):
    - 1 participant at Day 59 (63 copies/mL detected 3 days after Vaccination 2). This adolescent participant (subject 3357) had no detectable viraemia after the 1st vaccination and had saliva shedding >LLOD detected only on Day 14 (220 copies/mL).
    - 2 participants at Day 98, which correspond to 42 days after Vaccination 2. Subject 3068 (adult) had 259 copies/mL detected at visit 12, but had no detectable levels of viraemia nor shedding at any other time-point tested. Subject 3360 (adolescent) had 100 copies/mL

detected at visit 12 and had relatively low levels of viraemia and shedding detected after the 1st dose (25 copies/mL in plasma at Day 28 and 128 copies/mL in saliva at Day 7).

- There was no detectable shedding ≥LLOD cutoff values in saliva or urine samples (*Table 34*).

No participant in the pooled placebo group had detectable viremia or shedding of V920 (Table 32).

Table 32: Viremia or Shedding of Vaccine Virus (RNA Copies/mL) by Vaccination Group Over Time in Blood, Urine, or Saliva With LLOD Cutoffs (All Participants as Treated – Cohort 1 to Cohort 5)

Time Point	V920 1 Dose[a] (N=161) Percent (m/n) [95% CI]	V920 2 Dose[b] (N=40) Percent (m/n) [95% CI]	Pooled V920[c] (N=201) Percent (m/n) [95% CI]	Placebo[c] (N=49) Percent (m/n) [95% CI]
At any time	83.9 (135/161) [77.2%, 89.2%]	77.5 (31/40) [61.5%, 89.2%]	82.6 (166/201) [76.6%, 87.6%]	0.0 (0/48) [0.0%, 7.4%]
Day 3	83.2 (134/161) [76.5%, 88.6%]	65.0 (26/40) [48.3%, 79.4%]	79.6 (160/201) [73.4%, 84.9%]	0.0 (0/48) [0.0%, 7.4%]
Day 7	20.5 (33/161) [14.5%, 27.6%]	15.0 (6/40) [5.7%, 29.8%]	19.4 (39/201) [14.2%, 25.6%]	0.0 (0/48) [0.0%, 7.4%]
Day 14	9.9 (16/161) [5.8%, 15.6%]	12.8 (5/39) [4.3%, 27.4%]	10.5 (21/200) [6.6%, 15.6%]	0.0 (0/48) [0.0%, 7.4%]
Day 28	1.2 (2/161) [0.2%, 4.4%]	2.5 (1/40) [0.1%, 13.2%]	1.5 (3/201) [0.3%, 4.3%]	0.0 (0/48) [0.0%, 7.4%]
Day 42	0.0 (0/161) [0.0%, 2.3%]	0.0 (0/40) [0.0%, 8.8%]	0.0 (0/201) [0.0%, 1.8%]	0.0 (0/48) [0.0%, 7.4%]
Day 56[b]		0.0 (0/40) [0.0%, 8.8%]	0.0 (0/40) [0.0%, 8.8%]	0.0 (0/10) [0.0%, 30.8%]
Day 59[b]		2.5 (1/40) [0.1%, 13.2%]	2.5 (1/40) [0.1%, 13.2%]	0.0 (0/10) [0.0%, 30.8%]
Day 63[b]		0.0 (0/40) [0.0%, 8.8%]	0.0 (0/40) [0.0%, 8.8%]	0.0 (0/10) [0.0%, 30.8%]
Day 70[b]		0.0 (0/40) [0.0%, 8.8%]	0.0 (0/40) [0.0%, 8.8%]	0.0 (0/10) [0.0%, 30.8%]
Day 84[b]		0.0 (0/40) [0.0%, 8.8%]	0.0 (0/40) [0.0%, 8.8%]	0.0 (0/10) [0.0%, 30.8%]
Day 98[b]		5.0 (2/40) [0.6%, 16.9%]	5.0 (2/40) [0.6%, 16.9%]	0.0 (0/10) [0.0%, 30.8%]

Percent=m/n and represents proportion of participants with viremia or shedding ≥7.8125 in blood, ≥7.8125 in urine, and ≥100 in saliva, where the cutoff values are the LLODs.
N=number of participants with shedding or viremia data at one or more timepoints according to the intervention to which they received.
n=number of participants contributing to the analysis. m=number of participants with shedding.
[a] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.
[b] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose.
[c] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose.
CI=confidence interval; RNA=ribonucleic acid; LLOD=lower limit of detection.

Table 33: Viremia of Vaccine Virus (RNA Copies/mL) by Vaccination Group Over Time in Blood with LLOD Cutoff (All Participants as Treated - Cohort 1 to Cohort 5)

Time Point	V920 1 Dose[a] (N=161) Percent (m/n) [95% CI]	V920 2 Dose[b] (N=40) Percent (m/n) [95% CI]	Pooled V920[c] (N=201) Percent (m/n) [95% CI]	Placebo[c] (N=49) Percent (m/n) [95% CI]
At any time	82.6 (133/161) [75.9%, 88.1%]	75.0 (30/40) [58.8%, 87.3%]	81.1 (163/201) [75.0%, 86.3%]	0.0 (0/48) [0.0%, 7.4%]
Day 3	83.1 (133/160) [76.4%, 88.6%]	65.0 (26/40) [48.3%, 79.4%]	79.5 (159/200) [73.2%, 84.9%]	0.0 (0/48) [0.0%, 7.4%]
Day 7	3.1 (5/161) [1.0%, 7.1%]	2.5 (1/40) [0.1%, 13.2%]	3.0 (6/201) [1.1%, 6.4%]	0.0 (0/48) [0.0%, 7.4%]
Day 14	0.0 (0/161) [0.0%, 2.3%]	0.0 (0/39) [0.0%, 9.0%]	0.0 (0/200) [0.0%, 1.8%]	0.0 (0/48) [0.0%, 7.4%]
Day 28	1.3 (2/158) [0.2%, 4.5%]	2.5 (1/40) [0.1%, 13.2%]	1.5 (3/198) [0.3%, 4.4%]	0.0 (0/47) [0.0%, 7.5%]
Day 42	0.0 (0/161) [0.0%, 2.3%]	0.0 (0/40) [0.0%, 8.8%]	0.0 (0/201) [0.0%, 1.8%]	0.0 (0/47) [0.0%, 7.5%]
Day 56[b]		0.0 (0/40) [0.0%, 8.8%]	0.0 (0/40) [0.0%, 8.8%]	0.0 (0/10) [0.0%, 30.8%]
Day 59[b]		2.5 (1/40) [0.1%, 13.2%]	2.5 (1/40) [0.1%, 13.2%]	0.0 (0/10) [0.0%, 30.8%]
Day 63[b]		0.0 (0/40) [0.0%, 8.8%]	0.0 (0/40) [0.0%, 8.8%]	0.0 (0/10) [0.0%, 30.8%]
Day 70[b]		0.0 (0/40) [0.0%, 8.8%]	0.0 (0/40) [0.0%, 8.8%]	0.0 (0/10) [0.0%, 30.8%]
Day 84[b]		0.0 (0/40) [0.0%, 8.8%]	0.0 (0/40) [0.0%, 8.8%]	0.0 (0/10) [0.0%, 30.8%]
Day 84[b]		5.0 (2/40) [0.6%, 16.9%]	5.0 (2/40) [0.6%, 16.9%]	0.0 (0/10) [0.0%, 30.8%]
Day 98[b]				

Percent=m/n and represents proportion of participants with viremia or shedding ≥7.8125 in blood, ≥7.8125 in urine, and ≥100 in saliva, where the cutoff values are the LLODs.
N=number of participants with shedding or viremia data at one or more timepoints according to the intervention to which they received.
n=number of participants contributing to the analysis. m=number of participants with shedding.
[a] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.
[b] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose.
[c] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose.
CI=confidence interval; RNA=ribonucleic acid; LLOD=lower limit of detection.

Table 34: Shedding of Vaccine Virus (RNA Copies/mL) by Vaccination Group Over Time in Saliva with LLOD Cutoff (All Participants as Treated - Cohort 1 to Cohort 5)

Time Point	V920 1 Dose[a] (N=161) Percent (m/n) [95% CI]	V920 2 Dose[b] (N=40) Percent (m/n) [95% CI]	Pooled V920[c] (N=201) Percent (m/n) [95% CI]	Placebo[c] (N=49) Percent (m/n) [95% CI]
At any time	23.0 (37/161) [16.7%, 30.3%]	22.5 (9/40) [10.8%, 38.5%]	22.9 (46/201) [17.3%, 29.3%]	0.0 (0/48) [0.0%, 7.4%]
Day 3	5.0 (8/160) [2.2%, 9.6%]	2.5 (1/40) [0.1%, 13.2%]	4.5 (9/200) [2.1%, 8.4%]	0.0 (0/47) [0.0%, 7.5%]
Day 7	17.5 (28/160) [12.0%, 24.3%]	12.5 (5/40) [4.2%, 26.8%]	16.5 (33/200) [11.6%, 22.4%]	0.0 (0/48) [0.0%, 7.4%]
Day 14	10.3 (16/156) [6.0%, 16.1%]	12.8 (5/39) [4.3%, 27.4%]	10.8 (21/195) [6.8%, 16.0%]	0.0 (0/48) [0.0%, 7.4%]
Day 28	0.0 (0/159) [0.0%, 2.3%]	0.0 (0/40) [0.0%, 8.8%]	0.0 (0/199) [0.0%, 1.8%]	0.0 (0/47) [0.0%, 7.5%]
Day 42	0.0 (0/159) [0.0%, 2.3%]	0.0 (0/40) [0.0%, 8.8%]	0.0 (0/199) [0.0%, 1.8%]	0.0 (0/47) [0.0%, 7.5%]
Day 56[b]		0.0 (0/36) [0.0%, 9.7%]	0.0 (0/36) [0.0%, 9.7%]	0.0 (0/9) [0.0%, 33.6%]
Day 59[b]		0.0 (0/40) [0.0%, 8.8%]	0.0 (0/40) [0.0%, 8.8%]	0.0 (0/10) [0.0%, 30.8%]
Day 63[b]		0.0 (0/40) [0.0%, 8.8%]	0.0 (0/40) [0.0%, 8.8%]	0.0 (0/10) [0.0%, 30.8%]
Day 70[b]		0.0 (0/40) [0.0%, 8.8%]	0.0 (0/40) [0.0%, 8.8%]	0.0 (0/10) [0.0%, 30.8%]
Day 84[b]		0.0 (0/40) [0.0%, 8.8%]	0.0 (0/40) [0.0%, 8.8%]	0.0 (0/10) [0.0%, 30.8%]
Day 84[b] Day 98[b]		0.0 (0/40) [0.0%, 8.8%]	0.0 (0/40) [0.0%, 8.8%]	0.0 (0/10) [0.0%, 30.8%]

Percent=m/n and represents proportion of participants with viremia or shedding ≥7.8125 in blood, ≥7.8125 in urine, and ≥100 in saliva, where the cutoff values are the LLODs.
N=number of participants with shedding or viremia data at one or more timepoints according to the intervention to which they received.
n=number of participants contributing to the analysis. m=number of participants with shedding.
[a] V920 1 Dose=V920 1 Dose Treatment Group: Cohort 1 Adults CD4≥500 1 dose. Cohort 2 Adults CD4 >350 and <500 1 dose. Cohort 3 Adults CD4 ≥200 and ≤350 1 dose. Cohort 4 Adolescents CD4≥200 1 dose.
[b] V920 2 Dose=V920 2 Dose Treatment Group: Cohort 5 Adults and adolescents CD4≥200 2 dose.
[c] Cohorts 1-5 Adults and adolescents CD4≥200 1 or 2 dose.
CI=confidence interval; RNA=ribonucleic acid; LLOD=lower limit of detection.

7.2.6. Vital signs and physical findings

Vital-signs measurements were collected at screening/baseline and on Vaccination Day (Day 0; postvaccination); Days 3, 7, 14, 28, 42, 56, 59, 63, 70, 84, and 98; Months 6 and 12; and at study exit. Participants were prompted to report body temperatures for 42 days after vaccination starting with the day of vaccination (after each vaccination for Cohort 5).

There were no clinically meaningful findings in vital-signs measurements (blood pressure, heart rate, and respiratory rate).

In the pooled V920 group, 10.4% of participants had a maximum temperature ≥38.0° C (≥100.4° F) in the 42 days postvaccination (Vaccination 1 for Cohort 5) (versus 0% in placebo).

In the 2-dose V920 group (cohort 5), the proportions of participants who a maximum temperature ≥38.0° C (≥100.4° F) in the 42 days postvaccination after the 1st vaccination was higher (7.5%) than within 42 days after the 2nd (2.5% - 1 participant).

7.2.7. Safety in special groups and situations

7.2.7.1. Intrinsic Factors

CD4 T-cell counts

Overall, some small non-clinically relevant differences were observed between cohort 1 and cohort 3:

- Cohort 1 (CD4 ≥500 cells/mm3): 51 adults (41 vaccinated with V920, 10 with placebo)
- Cohort 3 (CD4 ≥200 cells/mm3 and ≤350 cells/mm3): 50 adults (41 vaccinated with V920, 9 with placebo)

The biggest difference was observed in V920 group for the related solicited systemic AE with a frequency lower in cohort 1 (52.5% vs. 30% in placebo) than in cohort 3 (70.7% vs. 22.2% in placebo) (CSR tables 14.3-42 and 14.3-44). This was mainly driven by the reported related fatigue (cohort 1: 27.5% vs. 10% in placebo) (cohort 5: 51.2% vs. 0, respectively) and reported related headache (cohort 1: 25% vs. 20% in placebo) (cohort 5: 46.3% vs. 11.1%, respectively).

Adults and adolescents

The frequencies of AE within the 42-days postvaccination were slightly higher in adolescents (cohorts 4 and 5) than in adults (cohorts 1 to 3 and 5) for both the V920 group (96.2% and 92.6%, respectively) and placebo group (84.6% and 72.2%) (CSR tables 14.3-9 and 14.3-10).

The frequencies of solicited AE within the 14 days postvaccination were slightly higher in adolescents (cohorts 4 and 5) than in adults (cohorts 1 to 3 and 5) for both the V920 group (92.3% and 86.6%, respectively) and placebo group (84.6% and 52.8%) (CSR tables 14.3-35 and 14.3-36). This trends was driven by the solicited local AE, and in particular, by the frequencies of injection site pain:

- Local: V920 group (88.5% and 59.1%, respectively) and placebo group (38.5% and 25%); with injection site pain: V920 group (86.5% and 57%, respectively) and placebo group (30.8% and 22.2%)
- Systemic: V920 group (67.3% and 77.9%, respectively) and placebo group (69.2% and 47.2%).

The frequencies of related solicited AE within the 14 days postvaccination were also slightly higher in adolescents (cohorts 4 and 5) than in adults (cohorts 1 to 3 and 5) for both the V920 group (90.4% and 81.9%, respectively) and placebo group (46.2% and 38.9%) (CSR tables 14.3-48 and 14.3-49). The frequencies of the related solicited local AE were identical than the frequencies of all solicited local AE (as they were all assessed as related). However, in both groups, the frequencies of the related solicited systemic AE were much lower in the adolescents versus then adults: V920 group (17.3% and 60.4%, respectively) and placebo group (7.7% and 30.6%).

The frequencies of solicited events specific to postvaccination within 42 days after vaccination were higher in adults (cohorts 1 to 3 and 5) than in adolescents (cohorts 4 and 5) for both the V920 group (41.6% and 21.2%, respectively) and placebo group (27.8% and 7.7%) (CSR tables 14.3-63 and 14.3-64). This trends was driven by the frequencies of arthralgia: V920 group (36.9% and 5.8%, respectively) and placebo group (22.2% and 0%).

The frequencies of related solicited events specific to postvaccination within 42 days after vaccination were also higher in adults (cohorts 1 to 3 and 5) than in adolescents (cohorts 4 and 5) for both the V920 group (32.2% and 17.3%, respectively) and placebo group (13.9% and 0%) (CSR tables 14.3-75 and 14.3-76). This trends was driven by the frequencies of arthralgia: V920 group (24.2% and 0%, respectively) and placebo group (13.9% and 0%).

The frequencies of unsolicited AE within the 42 days postvaccination were slightly higher in adolescents (cohorts 4 and 5) than in adults (cohorts 1 to 3 and 5) in the V920 group (65.4% and 47.7%, respectively), but not in the placebo group (38.5% and 47.2%, respectively) (CSR tables 14.3-89 and 14.3-90). This trends was driven by the frequencies of cough: V920 group (17.3% and 2%, respectively) and placebo group (15.4% and 5.6%).

The frequencies of related unsolicited AE within the 42 days postvaccination were similar in the adolescents (cohorts 4 and 5) and adults (cohorts 1 to 3 and 5) in the V920 group (11.5% and 11.4%, respectively), but not in the placebo group (23.1% and 11.1%, respectively).

Males and females

The frequencies of AE within the 42-days postvaccination were similar in females and males for the V920 group (94% and 93.1%, respectively) (placebo group: 80% and 68.4%, respectively). Similar trend was observed for the frequencies of solicited AE within the 14 days postvaccination in the V920 group (87% and 89.1%, respectively) (placebo group: 66.7% and 52.6%, respectively) with, in the V920 group, similar frequencies of local solicited AE (64% and 69.3%, respectively) and systemic solicited AE (73% and 77.2%, respectively).

The frequencies of related solicited AE within the 14 days postvaccination were also similar in females and males for the V920 group (82% and 86.1%, respectively) (placebo group: 46.7% and 31.6%, respectively), with, in the V920 group, similar frequencies of related local solicited AE (64% and 69.3%, respectively) and related systemic solicited AE (48% and 50.5%, respectively).

The frequencies of solicited events specific to postvaccination within 42 days after vaccination were also similar in females and males for the V920 group (37% and 35.6%, respectively) (placebo group: 33.3% and 5.3%, respectively), with, in the V920 group, similar frequencies of related solicited events specific to postvaccination within 42 days after vaccination (26% and 30.7%, respectively).

The frequencies of unsolicited AE within the 42 days postvaccination were higher in females than in males in the V920 group (62% and 42.6%, respectively) and in the placebo group (56.7% and 26.3%, respectively). For example, there were an increased frequencies of malaria: V920 group (8% and 5%, respectively) and placebo group (6.7% and 0%); rhinitis: V920 group (7% and 5%, respectively) and placebo group (3.3% and 0%); and headache: V920 group (8% and 2%, respectively) and placebo group (3.3% and 0%).

The frequencies of related unsolicited AE within the 42 days postvaccination were also higher in females than in males in the V920 group (16% and 6.9%, respectively) and in the placebo group (20% and 5.3%, respectively). However, there were no clear differences per PT.

7.2.7.2. Extrinsic Factors

The MAH submitted analysis for the participants in Burkina Faso and Senegal (181 in total) versus the participants in Canada (20). As this number of participants in Canada is very low, analysis will not be discussed here.

7.2.7.3. Drug Interactions

V920 was not administered concomitantly with any other vaccines in the V920-015 study; therefore, vaccine interactions were not evaluated.

7.2.7.4. Use in Pregnancy and Lactation

No pregnancies or lactation were reported for any participant in this study.

7.2.7.5. Overdose and drug abuse

There were no reports of overdose or abuse of V920 in the V920-015 study.

7.3. Discussion

Adolescents and adults 13 to 70 years of age (inclusive) living with HIV received either 1 or 2 doses of V920 or placebo and were followed for safety through 1 year after vaccination (1 year after first vaccination for those in the 2-dose group). A total of 250 participants in Cohorts 1 to 5 (201 in the pooled V920 group, 49 in the pooled placebo group) were included in the safety population (including in the V920 group: 52 adolescents and 149 adults; 100 females and 101 males).

In the pooled V920 group (Cohorts 1 to 5 combined), the reported common injection-site adverse reactions reported within 14 days postvaccination (Vaccination 1 for Cohort 5) were injection-site pain (64.7%), swelling (5.5%), and erythema (4.5%). The reported systemic adverse reactions were headache (54.2%), fatigue (45.3%), feeling hot (25.4%), arthralgia (24.9%), myalgia (17.4%), chills (16.4%), nausea (13.9%), hyperhidrosis (12.9%), abdominal pain (12.4%), diarrhoea (8.5%), pyrexia (5.5%), rash (4%), and blister (1%).

In the pooled V920 group, the frequencies of the reported solicited events specific to postvaccination within 42 days after vaccination are, overall, slightly higher than the frequencies observed 14 days after vaccination: arthralgia (28.9%), pyrexia (10.4%), rash (6%), and blister (1.5%).

All these solicited AEs have been described in the SmPC section 4.8 after injection with Ervebo in healthy volunteers with similar frequencies.

The frequencies observed after 1 year postvaccination (1 year after Vaccination 1 for Cohort 5) where similar to those at 42-days postvaccination (after Vaccination 1 for Cohort 5), and no clinically meaningful unsolicited event has been reported.

Overall, some small non-clinically relevant differences were observed between cohort 1 (CD4 $\geq$500 cells/mm3) and cohort 3 (CD4 $\geq$200 cells/mm3 and $\leq$350 cells/mm3). In particular, related fatigue and headache were more reported in cohort 3 versus cohort 1. However, the sample size of the groups were too small to make definitive conclusion (per group: around 40 vaccinated with V920 and 10 with placebo).

Therefore, in this study 015, the safety profile of the V920 vaccine in 52 adolescents and 149 adults living with HIV on antiretroviral therapy with a CD4+ T-lymphocyte count greater than or equal to 200 cells/mm3 was generally consistent with the known safety profile of Ervebo.

Safety analyses were additionally presented by subgroup by age category (adults or adolescents) and sex (males or females). Overall, no clinically meaningful differences in AE profiles were observed. However, the results should be interpreted with caution due to the small sample sizes in the subgroups (52 adolescents and 149 adults; 100 females and 101 males).

Concerning vaccine viraemia and shedding in saliva and urine post-vaccination, a qualified Quantitative Real-time Reverse Transcription Polymerase Chain Reaction Assay (qRT-PCR) was applied that is comparable to the one applied to assess viraemia and shedding in previous V920 clinical studies, such as V920-016 PREVAC trial. Results in terms of proportions of participants with viremia or shedding at different time-point post-vaccination were submitted. As compared to already available data concerning proportions of subject with positive vaccine viraemia or shedding in saliva after ERVEBO vaccination, no major differences were noted in that respect in participants of V920-015. The MAH also submitted quantitative data and individual trajectories of copies/mL over time. Collectively, viraemia and shedding results from V920-015 do not indicate notable differences as compared to previous clinical trials in terms of proportion of positive subjects, kinetics of vaccine viraemia and shedding, quantitative data in adolescents and adults 13 to 70 years of age (inclusive) living with HIV.

8. Risk management plan

The MAH submitted an updated RMP version with this application. The (main) proposed RMP changes were the following:

- Include study data following the completion of V920-015, to remove V920-015 as an additional pharmacovigilance (PV) activity, and to remove *'Exposure in HIV-Infected Individuals'* as Missing Information.

- Include data from Expanded Access Protocol 5 (EAP5) and to remove EAP5 as an additional PV activity.

The significant changes in this RMP encompass updated epidemiology information, incorporation of clinical trial data from study V920-015 throughout the document, inclusion of Expanded Access Protocol 5 (EAP5) data, and the removal of V920-015 and EAP5 as additional PV activities in Part V. *'Exposure in HIV-Infected Individuals'* has been removed from the list of Missing Information.

Summary of the safety concerns

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Viral shedding/secondary transmission to close contacts, particularly immunocompromised hosts
Missing information	• Exposure during pregnancy • Exposure during lactation • ~~Exposure in HIV-infected individuals~~

The following information regarding exposure in Expanded Access Protocol 005 [EAP5] was added in *Table SIV 3.1 Exposure of Special Populations Included or not in Clinical Trial Development Programs*:

'Patients with HIV and/or AIDS

…

A total of 201 adolescents and adults living with HIV (CD4 T-Cell counts ⩾200 cells/mm3 on antiretroviral therapy with an undetectable viral load [<40 copies/mL]) were vaccinated with rVSV∆G-ZEBOV-GP in V920-015.'

'Pregnant or breastfeeding women

…

The rVSVΔG-ZEBOV-GP vaccine was administered in the context of Expanded Access Protocol 005 ([hereafter referred to as EAP5] Compassionate ring vaccination study sponsored by the DRC Ministry of Public Health, WHO, and MSF to evaluate the safety of the Ebola vaccine in the DRC) from AUG-2018 through JUN-2020 in an outbreak setting and during a complex humanitarian situation. In JUN-2019, the protocol was amended so that pregnant individuals after the first trimester and lactating individuals were eligible for inclusion and vaccination.

A total of 1882 vaccinees were reported to be pregnant or lactating at time of vaccination; 22 of 1882 pregnant or lactating vaccinees were reported to develop EVD, and there is no further information

regarding lactating vaccinees. No safety information was provided regarding lactating vaccinees.

Pregnancy outcomes were available for 1509 vaccinated pregnant individuals; the majority were ≤35 years of age and were reported to be in either the second or third trimester of pregnancy. Other reported obstetric history was limited, and few individuals had a reported history of abortion, c-section, and hypertension.

The majority of individuals reported full-term deliveries [Ref. 5.4: 08RBCR]. A small number of participants reported abortions and stillbirths. Three of these pregnant vaccinees developed EVD, none of whom died. Two maternal deaths unrelated to EVD were reported and neither were considered related to vaccination by the investigator. Seven full-term and 1 pre-term perinatal deaths were reported. There are limitations to the completeness of the data collection given the challenging outbreak setting in which EAP5 was conducted.

…'

PRAC Rapporteur assessment comment:

The removal of the area of Missing information *'Exposure in HIV-Infected Individuals'* [and all related RMP parts] is consequential to the finalisation of the category 3 PASS V920-015 – see assessment of study data above – and is accepted.

The updates related to *Part II Modules SI Epidemiology*, *SIII Clinical trial exposure*, *SIV Populations not studied in clinical trials* [including exposure in EAP5], *SV Post-authorisation experience* are administrative, and accepted.

No further changes in the RMP summary of safety concerns are being proposed. This is accepted.

8.1. Overall conclusion on the RMP

☒ The changes to the RMP are acceptable. RMP version 3.0 is acceptable.

9. Changes to the Product Information

As a result of this variation, sections 4.4., 4.8, and 5.1 of the SmPC are being updated to include safety and immunogenicity data following the results from study V920-015.

In addition, the list of local representatives in the PL is being removed.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

10. Request for supplementary information

10.1. Major objections

None.

10.2. Other concerns

Clinical aspects

1. Applied assay methods to assess humoral immune responses (GP-ELISA and PRNT) and to assess viraemia and shedding and laboratories where assays were performed need to be confirmed. Detailed descriptions of the applied assays and of their status are expected if not yet submitted. Whether samples collected from participants from African sites were gamma-irradiated or not should be clarified.
2. In study V920-015, 3 different V920 Drug Product Lots were used, all had a potency ≥2 x 10E7 pfu/mL. Actual potency of the 3 lots and distribution by cohort/country were not provided and should be submitted for completeness.
3. An unexpected trend of an increase in GP-ELISA GMTs at Month 6 and Month 12 as compared to Day 28 GMT in the combined 1-dose cohorts is noted (also reflected in terms of GP-ELISA GMFIs results). Similarly, a trend towards an increase in PRNT GMT at Month 12 as compared to Day 28 GMT after 1 dose of V920 is noted (also reflected in terms of PRNT GMFIs results). The MAH should clarify and further discuss these unexpected trends also by taking into consideration the data presented by cohort, and separately for participants from African and Canadian clinical sites.
4. Quantitative viremia and shedding data and individual trajectories of copies/mL over time should be submitted.

RMP aspects

None.

11. Assessment of the responses to the request for supplementary information

11.1. Major objections

Not applicable.

11.2. Other concerns

Clinical aspects

Question 1

Applied assay methods to assess humoral immune responses (GP-ELISA and PRNT) and to assess viraemia and shedding and laboratories where assays were performed need to be confirmed. Detailed descriptions of the applied assays and of their status are expected if not yet submitted. Whether samples collected from participants from African sites were gamma-irradiated or not should be clarified.

Summary of the MAH's response

The MAH specified that immunogenicity results reported for V920-015 were generated from a validated proprietary glycoprotein enzyme-linked immunosorbent assay GP-ELISA, and a validated plaque reduction neutralization test (PRNT).

The MAH clarified that samples collected from participants from African sites were not gamma-irradiated.

The MAH clarified that viraemia and shedding results reported for V920-015 were generated from a qualified Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) assay.

All assays were performed at Q2 Solutions/IQVIA Laboratories at 2 locations in the US and have been used in V920 Protocols -009, -012, -016 and -018.

The MAH provided brief assay descriptions that have been included in the corresponding sections when needed.

Assessment of the MAH's response

The MAH did not submit detailed descriptions of the applied assays as requested but provided brief assay descriptions. However this is deemed acceptable, considering that the MAH clarified that the applied assays have been used in V920 Protocols -009, -012, -016 and -018 and hence were already assessed in different procedures.

The MAH clarified that samples collected from participants from African sites were not gamma-irradiated.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 2

In study V920-015, 3 different V920 Drug Product Lots were used, all had a potency ⩾2 x 10E7 pfu/mL. Actual potency of the 3 lots and distribution by cohort/country were not provided and should be submitted for completeness.

Summary of the MAH's response

The MAH provided V920 drug lot numbers, actual potencies, and specified to which country each lot was shipped (Table below)

Lot Number	Potency[1]	Country Vaccine Shipped To
WL00067464 (underlying drug product lot WL00063635)	1.3 x 10^8 pfu/mL	Burkina Faso, Senegal
0000852249 (underlying drug product lot WL00067929)	3.0 x 10^8 pfu/mL	Burkina Faso, Senegal, Canada
WL00061392 (underlying drug product lot WL00061283)	5.4 x 10^7 pfu/mL	Canada
[1] Per Certificate of Analysis at release		

Data on distribution of the different lots by cohort/country are not compiled and were therefore not submitted.

Assessment of the MAH's response

The MAH submitted the requested information on the 3 different V920 Drug Product Lots applied (V920 drug lot numbers, actual potencies, and to which country each lot was shipped). Data on distribution of the different lots by cohort/country are not available (not compiled) and were therefore not submitted. This is a limitation given the differences in potency of the different lots, ranging from 5.4 x 10E7 pfu/mL to 3.0 x 10E8 pfu/mL.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 3

An unexpected trend of an increase in GP-ELISA GMTs at Month 6 and Month 12 as compared to Day 28 GMT in the combined 1-dose cohorts is noted (also reflected in terms of GP-ELISA GMFIs results). Similarly, a trend towards an increase in PRNT GMT at Month 12 as compared to Day 28 GMT after 1 dose of V920 is noted (also reflected in terms of PRNT GMFIs results). The MAH should clarify and further discuss these unexpected trends also by taking into consideration the data presented by cohort, and separately for participants from African and Canadian clinical sites.

Summary of the MAH's response

The MAH specified in their answer that the overall kinetics of the GP-ELISA and PRNT responses are consistent with previously reported V920 clinical studies and with nonhuman primate data when tested in the same validated assays.

Suggestion of a trend of increase in GP-ELISA and PRNT responses after Day 28 has been observed in both human and NHP studies; it has been observed more frequently in PRNT responses. In clinical studies, these findings have been observed in children and adults, including adults >50 years of age and in trial participants in both African and ex-African countries. Although this study was not powered to make direct comparisons among different time points or by subgroup, these findings are biologically plausible and may be associated with maturation of the immune response. Thus, the observed increase in antibody titers at later time points may be explained by the natural maturation and evolution of the immune response following vaccination. This process can result in a gradual increase or sustained elevation of antibody titers months after vaccination, even in the absence of additional antigen exposure.

In support of their hypothesis to explain the observed unexpected trends, the MAH referred to two publications related to germinal centres (Mesin et al.; Immunity. 2016 Sep 20;45:471-82 and Victora et al.; Annu Rev Immunol. 2012;30:429-57.

Finally, the MAH specified that the validated assays are conducted with appropriate controls to monitor expected performance across assay runs and the trends are consistent across participants and studies regardless of the assay run.

Assessment of the MAH's response

The MAH speculated that the unexpected trends in antibody responses might be associated with maturation of the immune response, which can result in a gradual increase or sustained elevation of antibody titers months after vaccination, even in the absence of additional antigen exposure.

It is agreed with the MAH, that these unexpected trends were also notable in other clinical studies and were also discussed at the time of EoI to include infants >1 YoA in the indication. Nevertheless, these unexpected trends appear more pronounced in study V920-015 and the MAH did not discuss if differences in CD4+ T cell counts in the different cohorts or differences in recruitment country might have had an impact on this aspect.

The MAH specified that these unexpected trends in kinetic of antibody responses cannot be attributed to the applied ELISA and PRNT assays, this is acknowledged.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 4

Quantitative viraemia and shedding data and individual trajectories of copies/mL over time should be submitted.

Summary of the MAH's response

The MAH submitted figures representing quantitative viraemia and shedding data over time (Figures below) and individual vaccine viraemia and shedding listings.

Figure 1
Viremia of Vaccine Virus by Vaccination Group Over Time in Plasma
(All Participants as Treated)
(Cohort 1 to Cohort 5)

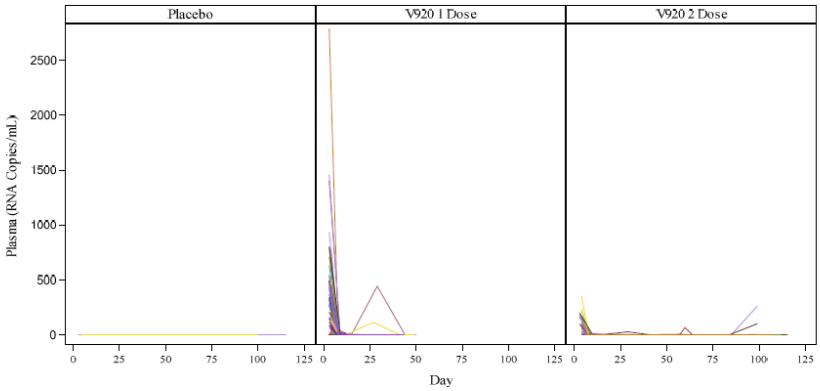


Figure 2
Shedding of Vaccine Virus by Vaccination Group Over Time in Saliva
(All Participants as Treated)
(Cohort 1 to Cohort 5)

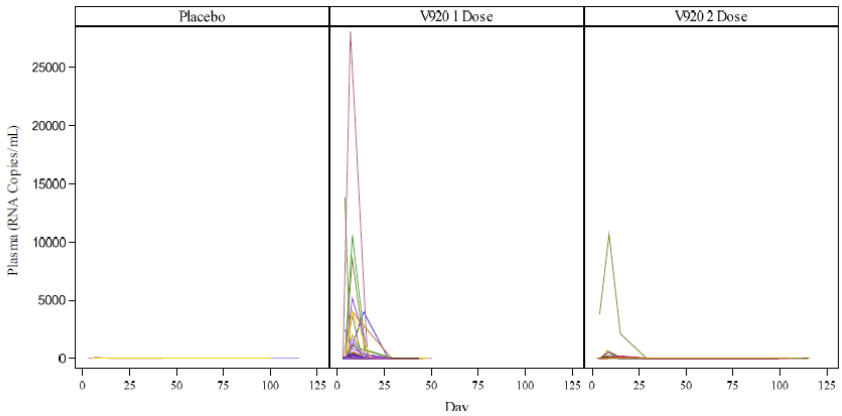
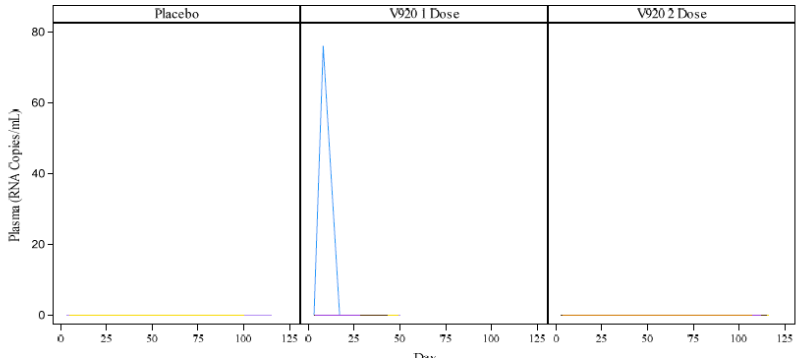


Figure 3
Shedding of Vaccine Virus by Vaccination Group Over Time in Urine
(All Participants as Treated)
(Cohort 1 to Cohort 5)



Assessment of the MAH's response

The MAH submitted the requested quantitative viraemia and shedding data and individual trajectories of copies/mL over time.

These overall do not indicate major differences in terms of vaccine viraemia nor saliva/urine shedding in the adolescent and adult participants (13-70 YoA) living with HIV of study V920-015 as compared to data already available and assessed in different procedures (marketing authorisation, extension of indication).

Based on the submitted results, proposed amendment to the SmPC concerning shedding are deemed acceptable.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance