20 July 2023
EMA/372877/2023

Extension of indication variation assessment report

Invented name: Ervebo

Common name: recombinant vesicular stomatitis virus - Zaire Ebolavirus vaccine (live)

Procedure No. EMEA/H/C/004554/II/0025

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.

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List of abbreviations

4PL	4-Parameter Logistic
ACHIV	African-Canadian Study of HIV-Infected Adults and a Vaccine for Ebola
ADR	Adverse Drug Reaction
Ad26.ZEBOV	Adenovirus serotype 26 vector expressing the glycoprotein of the Ebola virus Mayinga variant (vaccine)
AE	Adverse Event
ANOVA	Analysis of variance
ASaT	All Subjects as Treated
APaT	All Participants as Treated
AR	Adverse Reaction
ATC	Anatomical Therapeutic Chemical
BDS	Bulk Drug Substance
BMI	Body Mass Index
CAPA	Corrective Action and Preventive Action
CBC	Completed Blood Count
CCSI	Company Core Safety Information
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
Cmax	Maximum concentration
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome
CRF	Case Report Form
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
CV	Coefficient of Variation
DRC	Democratic Republic of the Congo
DSMB	Data Safety Monitoring Board
EBOV	Ebola Virus
eCRF	electronic Case Report Form
EEA	European Economic Area
ELISA	Enzyme-Linked ImmunoSorbent Assay
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ERC	Ethics Review Committee
EU	European Union
EURD	European Union Reference Date
EVD	Ebola Virus Disease
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPE	First participant Enrolled
GCP	Good Clinical Practice
GMFI	Geometric Mean Fold Increase
GMR	Geometric Mean Ratio
GMT	Geometric Mean Tier
GP	Glycoprotein
GP-EBOV	Ebola Virus Glycoprotein
GP-ELISA	Glycoprotein Enzyme-Linked ImmunoSorbent Assay
GPvP	Good Pharmacovigilance Practice
HIV	Human Immunodeficiency Virus

HR	Heart Rate
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICP	Immunological Correlates of Protection
ID	Identification
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
Kb	kilobases
LB	Lower Bound
LLOD	Lower Limit Of Detection
LLOQ	Lower Limit Of Quantification
LPLV	Last Participant Last Visit
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
mL	Millilitres
MRL	Merck Research Laboratories
MSD	Merck, Sharp & Dohme Corp.
MVA	Modified Vaccinia Ankara
MVA-BN-Filo	Modified Vaccinia Ankara Bavarian Nordic vector expressing multiple filovirus proteins (vaccine)
nAb	Neutralising antibody
NC	Nucleocapside
NCT	National Clinical Trial (USA)
NHP	Non-Human Primate
Nm	nanometre
NP	Nucleoprotein
OC	Optical Density
PDCO	Paediatric Committee
Pfu	Plaque-forming units
PHEIC	Public Health Emergency of International Concern
PI	Principal Investigator
PID	Participant Identification code
PIP	Paediatric Investigation Plan
PP	Per-Protocol
PRAC	Pharmacovigilance Risk Assessment Committee
PREVAC	Partnership for Research on Ebola Vaccination
PRNT	Plaque Reduction Neutralisation Test
PT	Preferred Term
qRT-PCR	Quantitative Real-time Reverse Transcription Polymerase Chain Reaction Assay
RCD	Reverse Cumulative Distribution
REC	Recommendation
rGP	Recombinant Glycoprotein
rHAd26/MVA	Ad26.ZEBOV prime/MVA-BN-Filo boost (vaccine)

rHSA	recombinant Human Serum Albumin
RMP	Risk Management Plan
RNA	Ribonucleic Acid
RT-PCR	reverse transcriptase polymerase chain reaction assay
rVSV	Recombinant vesicular stomatitis
rVSVΔG-ZEBOV-GP	Recombinant vesicular stomatitis virus-Zaire Ebola virus envelope glycoprotein (vaccine)
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SAWP	Scientific Advice Working Party
SC	Subcutaneous
SD	Standard Deviation
SDV	Source Document Verification
SDR	Source Data Review
SID	Syringe Identification Number
SOP	Standard Operating Procedure
ULN	Upper Limit of Normal
US	United States
USP	United States Pharmacopeia
VSV	Vesicular Stomatitis Virus
WHO	World Health Organisation
ZEBOV	Ebola Zaire virus
ZEBOV-rGP	Ebola Zaire vírus recombinante glycoprotein

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 19 July 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the paediatric population from 1 year to less than 18 years of age based on final results from study V920-016 (PREVAC); this is a phase 2, randomized, double-blind, placebo-controlled study of 2 leading Ebola vaccine candidates (Ad26.ZEBOV/MVA-BN-Filo and V920) and 3 vaccine strategies (Ad26.ZEBOV/MVABN-Filo, 1-dose V920, and 2 dose V920) to evaluate immunogenicity and safety in healthy children and adolescents from 1 to 17 years of age and adults 18 years of age and older. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to update the Annex II and the list of local representatives in the Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0429/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0429/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Christophe Focke Co-Rapporteur: Not Applicable

Timetable	Actual dates
Submission date	19 July 2022
Start of procedure:	13 August 2022
CHMP Rapporteur Assessment Report	7 October 2022
PRAC Rapporteur Assessment Report	12 October 2022
PRAC members comments	19 October 2022
Updated PRAC Rapporteur Assessment Report	24 October 2022
PRAC Outcome	27 October 2022
CHMP members comments	28 October 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	3 November 2022
Request for supplementary information (RSI)	10 November 2022
MAH's responses	22 February 2022
CHMP Rapporteur Assessment Report	28 March 2023
PRAC Rapporteur Assessment Report	28 March 2023
PRAC members comments	4 April 2023
Updated PRAC Rapporteur Assessment Report	20 April 2023
PRAC Outcome	14 April 2023
CHMP members comments	17 April 2023
Updated CHMP Rapporteur Assessment Report	20 April 2023
Request for supplementary information (RSI)	26 April 2023
Extension of timetable adopted	25 May 2023
MAH's responses	19 June 2023
CHMP Rapporteur Assessment Report	05 July 2023
CHMP members comments	10 July 2023
Updated CHMP Rapporteur Assessment Report	13 July 2023
CHMP Opinion	20 July 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Ebola Virus Disease (EVD) is an acute systemic febrile syndrome caused by Ebola Virus (EBOV). To date, six species of EBOV have been identified: Zaïre, Bundibugyo, Sudan, Taï Forest, Reston and Bombali, with the first four known to cause human disease. Case fatality of EVD varies with the EBOV species and ranges from 25% to 90% and incubation period ranges from 2 to 21 days. The disease-to-infection ratio is generally described as being 1:1 but some EVD asymptomatic and pauci-symptomatic infections are increasingly acknowledged.

While, historically, children have represented a small number of total cases of EVD, in recent outbreaks up to a quarter of cases have been in children. The largest outbreak to date was in West Africa from 2013 to 2016. This multi-country outbreak of Zaïre EBOV which included cases outside Africa resulted in 28,616 cases, of whom approximately 18–20% were children, with a reported mortality rate of 42–63% in children <18 years and of 73–86% in children <5 years.

Younger children appear to have shorter mean incubation periods than adults, with an average of 7 days in children younger than 1 year, 8-9 days in children 1-9 years, and 11 days in patients aged 45 years or older. The disease in children also tends to have a shorter time course from symptom onset to hospitalisation and/or death compared to adults.

EBOV is highly contagious and spreads through human-to-human transmission directly or indirectly via blood or body fluids (e.g., urine, saliva, sweat, faeces, vomit, breast milk, and semen) of living or dead infected persons, or any soiled material. Most contacts are with close family members living in the same household. Vertical and sexual transmission through vaginal secretions, semen and breast milk can also occur as the virus can persist in these sites. The duration of persistence and the magnitude of risk of transmission through survivors is currently unknown.

The pathogenesis of EVD is characterised by an intense inflammatory process, impaired haemostasis, and capillary leaks, with mortality resulting from septic shock and multi-organ system failure. Initial signs and symptoms are nonspecific (e.g., fever, headache, myalgia, fatigue) and may mimic other more common conditions such as malaria. After a week, haemorrhagic manifestations can appear in more than half of the patients. EVD progresses with gastrointestinal symptoms, internal and external bleeding, and in some cases, rash, and neurologic involvement. The varying spectrum of EVD severity is increasingly described.

Claimed indication

The MAH claims an extension of Ervebo' s approved indication to children and adolescents from 1 to 17 years of age for active immunisation to protect against EVD caused by Zaire EBOV.

Epidemiology and risk factors, screening tools/prevention

Since the initial identification of EBOV in 1976, more than 25 outbreaks of Ebola disease have been reported, a majority caused by Zaïre EBOV and at least 6 caused by Sudan EBOV, mainly occurring in

sub-Saharan Africa, mostly in Sudan, Uganda, Democratic Republic of Congo, and Gabon. Most of these outbreaks have occurred in isolated rural areas, but the outbreak in Gulu in 2000 was in a semi-urban area of Uganda. It is conceivable that small outbreaks might not have been detected. The largest Ebola outbreak to date occurred from 2013 to 2016 in West Africa, predominantly affecting Guinea, Sierra Leone, and Liberia affecting both rural and urban areas with very high incidence and mortality (more than 28 000 cases with more than 11 000 deaths). Due to potential under-reporting the true burden might have been even higher. In this outbreak, the overall mean case fatality in confirmed cases with recorded clinical outcomes was 62,9%. The epidemic peaked in August through October 2014. In March 2016, the WHO declared the end of the PHEIC. Sierra Leone was declared free of Ebola transmission in March 2016. After a few sporadic cases in Liberia and Guinea in March/April 2016, these two countries were also declared free of Ebola transmission in June 2016.

Most recent outbreaks were declared in the Democratic Republic of Congo and were caused by Zaïre EBOV. Recently, on 20-Sep-2022, Uganda declared an outbreak of Ebola disease, caused by Sudan EBOV.

Beyond the direct morbidity and mortality due to Ebola, large outbreaks of the disease have indirect effects on population health based on the diversion of resources from programmes aimed at controlling other diseases of major importance.

EVD is not an airborne disease and only symptomatic patients are contagious. As transmission requires direct contact with bodily fluids, the risk of infection is considered very low if precautions are strictly followed. The probability that EU/EEA citizens living or travelling in EVD-affected areas will be exposed to the virus is low provided they adhere to recommended precautionary measures. Nosocomial transmission can occur. Healthcare workers can be infected through close contact with infected patients. However, health worker infections are preventable, and the risk for infection can be significantly reduced through the appropriate use of infection control precautions and adequate barrier procedures.

The risk of EBOV spreading from an EVD patient who arrives in the EU as result of a planned medical evacuation is considered extremely low. If a symptomatic case of EVD presents in an EU Member State, secondary transmission to the family and in healthcare facilities cannot be ruled out.

Aetiology and pathogenesis

Aetiology

EBOV belong to the genus Ebolavirus of the Filoviridae family in the order Mononegavirales. All members of this order possess a non-segmented, negative-sense RNA genome of 19 kb with seven open reading frames, that is encapsulated by the viral nucleoprotein (NP). The NP–RNA complex acts as the template for genome replication and assembles into a helical nucleocapsid (NC) along with accessory proteins. EBOV has a striking, filamentous structure of about 800 nm in length and 80 nm in diameter. The helical NC acquires an envelope by budding from the plasma membrane. The viral envelope contains spikes consisting of the glycoprotein (GP) trimer. This GP molecule achieves the combined functions of attachment to host cells, endosomal entry, and membrane fusion.

The genus Ebolavirus includes six distinct species. Zaire, Sudan, Bundibugyo and Taï Forest EBOV occur in Africa and cause serious illness in humans. Reston does not cause illness in humans and Bombali has been identified in bats, but it is unclear if it can cause disease in humans. The first three, Bundibugyo, Zaire, and Sudan EBOV have been associated with large outbreaks in Africa. EBOV persists in the environment in a still unidentified animal reservoir, most likely the fruit bats, which maintains the virus in an enzootic cycle. Human infection represents a sporadic event taking place in the context of a human animal interface. Transmission is mainly due to the contact with blood or body fluids from infected humans or animals.

Pathogenesis

The tropism of EBOV gives some clues as to pathogenic mechanisms. The major route of infection is through the mucosa or skin from where the virus reaches macrophages, monocytes, and dendritic cells, leading to spread to regional lymph nodes, liver, and spleen. Macrophages and monocytes stimulated by EBOV release "cytokine storm" thereby damaging tissues and blood vessels. Death occurs due to blood loss and/or coagulation. Coagulopathy occurs due to thrombocytopenia, loss of anticoagulant protein C, destruction of clotting factors, and due to the destruction of fibrin. Damage to blood vessels causes disseminated intravascular coagulation as well as renal failure. Antibodies developed against EBOV bind with the complement C1q and reach to the binding sites on dendritic cells and macrophages, leading to damage of these cells. Lesions related to EVD include extensive haemorrhages of the mucosa, necrosis of different organs like liver, kidney, testes, and ovaries. Necrotic foci with inflammatory cells can be found in hepatic lobules, and there may be multinucleated syncytia formation in the hepatic cells. Necrosis of red pulp and fibrin deposition are the characteristic lesions seen in the spleen. Splenic macrophages reveal big, acidophilic particles in their cytoplasm which are similar to intracytoplasmic inclusion bodies. Gastrointestinal tract shows mononuclear infiltration into the submucosa and lamina propria. Mild emphysema, oedema in the terminal alveoli, and stasis of blood can be noticed in the lung parenchyma. It has also been shown that macrophages in the chambers of the eye, brain, and epididymis are sites of viral persistence (sanctuary sites).

Clinical presentation and diagnosis

Clinical presentation

Adults

Following an incubation period of 2–21 days, EVD typically starts as a non-specific viral syndrome with abrupt onset. At this stage the most frequent symptoms are high fever, malaise, fatigue, and body aches. These symptoms usually develop after a few days into gastrointestinal symptoms including nausea, vomiting, and diarrhoea. These manifestations can range from mild-to-severe, with body fluid loss of up to 5–10 L/day. Other, rarer, symptoms are cough and dyspnoea, conjunctival injection, hiccups, or localised pain of chest, abdomen, muscles, or joints.

Part of the patients may recover from this stage, others however will experience deterioration of symptoms finally going into shock, possibly due to hypovolaemia and a systemic inflammatory response. Around this time, patients can present with haemorrhagic events, such as conjunctival bleeding, petechiae, gastrointestinal bleeding, mucosal haemorrhage. Neurological events are rare and include confusion, delirium, and convulsions. Cases of EVD-related encephalitis have been reported. Other late symptoms include dysphagia, throat pain, and oral ulcers. A maculopapular rash has been described. Exceptionally, sudden death can occur in recovering patients, possibly due to cardiac arrhythmias. If patients survive the stage of shock, gradual recovery can occur.

Laboratory features include variable degrees of anaemia and thrombocytopenia as well as changes in number and type of white blood cells. Renal dysfunction (in up to 50% of case) and substantial increases in liver enzymes are common. Likewise, creatine phosphokinase and amylase concentrations can be increased. Electrolyte abnormalities are common, especially hypokalaemia, hyponatraemia, and hypocalcaemia. Clotting tests can indicate a varying degree of intravascular coagulation. Metabolic acidosis can occur, particularly in cases of shock and renal failure.

High viral loads, combined with severe muscle breakdown and renal impairment, have consistently been predictive of death. Differences in severity of clinical events and outcome might exist between young

children, young adults, and older people. Pregnant women face higher mortality and risk of miscarriage and stillbirth. Clinical presentation can be aggravated by concurrent comorbidities and infections, such as malaria and bacterial sepsis. Clinical signs and symptoms have varied across the different Ebola outbreaks reported during the last decades.

Children

Clinically, many signs and symptoms of EVD in children are difficult to differentiate from other infections and these include fever, anorexia, weakness, diarrhoea, vomiting and abdominal pain. Based on the largest collection of EVD data reported to date (2014-2016 outbreak), children are more likely to present with constitutional and gastrointestinal symptoms as well as fever but less likely to report abdominal, chest, and joint pain than adults. Mortality is high (ranging from 42–63% in children <18 years), especially in children <5 years old (with rates of 73–86%).

Diagnosis

Diagnosis based on clinical symptoms can be difficult as clinical manifestations are like those of other infectious diseases such as malaria, typhoid fever and meningitis. Confirmation that symptoms are caused by EBOV infection are made using diagnostic laboratory methods: ELISA, antigen-capture detection tests, serum neutralization test, RT-PCR, electron microscopy, virus isolation by cell culture.

When patients with EVD present at a hospital, typically 3–6 days after the onset of the symptoms, the viral load is already high and detectable in the patient's blood by RT-PCR in most cases. Viral load peaks 3–7 days after the onset of symptoms. In fatal cases, viraemia is usually 10–100 fold higher than in survivors. IgG and IgM humoral responses develop in survivors but not in all fatal cases thus, diagnosing of EVD using serology is only possible in a fraction of symptomatic patients and requires seroconversion or a substantial increase in antibody titre in paired serum samples. However, serology is the method of choice to diagnose asymptomatic EBOV infections characterised by extremely low viraemia and development of IgG and IgM about 3 weeks after infection. Another technique also used for post-mortem diagnosis is antigen detection by immunohistochemistry on a skin biopsy.

During the acute phase of the disease and convalescence, viral RNA can be detected by RT-PCR in other body fluids, such as saliva, tears, sweat, breast milk, urine, CSF, ocular fluid, amniotic fluid, vaginal fluid, and seminal fluid. Viral RNA can remain detectable in these fluids after the RT-PCR on blood becomes negative. Irrespective of the severity of the acute disease, EBOV tends to persist, specifically in immunologically privileged sites (such as the eye, central nervous system, and testis) where antiviral immune response is less effective. Persistence is associated with clinical sequelae, disease reactivation, long-term virus shedding, and virus transmission. Virus found in the seminal fluid can still be infectious and be sexually transmitted for more than a year after disease onset. Cases of women transmitting the virus via breastfeeding have been reported, although the duration of infectivity by this route is unknown. Reports suggest that other reservoirs and other human-to-human transmission routes of persisting virus in humans could still be uncovered.

Management

Treatments

The US FDA approved 2 monoclonal antibody therapies, REGN-EB3 (Inmazeb) and ansuvimab (Ebanga), for the treatment of infection caused by ZEBOV in adult and paediatric patients. REGN-EB3 is a combination of 3 fully human monoclonal antibodies that received approval in October 2020. The 3 monoclonal antibodies bind simultaneously to non-overlapping epitopes on the EBOV GP yielding neutralising activity to prevent entry of the virus into the host cell. Ansuvimab is a human monoclonal

IgG1 antibody that received approval in December 2020. Ansuvimab blocks binding between the EBOV GP and host cell receptor protein in the late endosomes.

Both REGN-EB3 and ansuvimab are administered intravenously. Results from the PALM Phase 2/3 study showed a lower incidence in mortality at 28 days (primary endpoint) for participants treated with REGN-EB3 and participants treated with ansuvimab compared with participants in the control group treated with ZMapp, an experimental triple monoclonal antibody which had shown a favourable trend in survival in a previous study.

Nonetheless, 34% and 67% of patients with higher viral loads who received ansuvimab and REGN-EB3, respectively, in the study died and there remains an unmet medical need for more efficacious interventions.

Other vaccines

Ad26.ZEBOV/MVA-BN-Filo, also known as Zabdeno and Mvabea, respectively, is a 2-component vaccine regimen that was authorised under exceptional circumstances in the EU and prequalified by the WHO for the prevention of disease caused by ZEBOV in individuals 1 year of age and older. Ad26.ZEBOV is administered first followed by MVA-BN-Filo approximately 8 weeks later as a booster. Ad26.ZEBOV encodes the *Zaire ebolavirus* Mayinga variant GP. MVA-BN-Filo encodes 4 filovirus antigens, namely GP from *Zaire ebolavirus* Mayinga variant, GP from *Sudan ebolavirus* Gulu variant, GP from *Marburgvirus* Musoke variant, and the Nucleoprotein from *Taï Forest ebolavirus*. Clinical studies demonstrated that Ad26.ZEBOV/MVA-BN-Filo is safe and elicits strong neutralising and non-neutralising antibody responses. In the paediatric population vaccinated with Ad26.ZEBOV/MVA-BN-Filo, EBOV GP-specific binding antibody responses were tested in respectively 123 children aged 1-3 years (study EBL3001), 182 children aged 4-11 years (52 in study EBL2002 and 130 in study EBL3001), and in 195 adolescents aged 12-17 years (53 in study EBL2002 and 142 in study EBL3001). However, protective efficacy against EVD in humans has not been demonstrated. Also, the need for more than 1 dose and the length of time between doses make this vaccine regimen less suitable for an outbreak response in which immediate protection is necessary.

2.1.2. About the product

Ervebo vaccine (hereinafter also referred to as V920) is a recombinant vesicular stomatitis virus (rVSV) which has the gene encoding for the VSV glycoprotein G deleted from its RNA and replaced with the gene encoding for the ZEBOV (Kikwit strain) glycoprotein (rVSVΔG-ZEBOV-GP). The vaccine is a genetically engineered, replication-competent, attenuated live vaccine that induces immune responses after a single dose.

The relative contributions of innate, humoral and cell-mediated immune responses to protection from ZEBOV are unknown.

The pharmacotherapeutic group (ATC Code) is viral vaccines (J07BX02).

The vaccine is manufactured in serum-free Vero cell cultures. The virus is harvested from the cell culture medium, purified, and frozen to produce the Bulk Drug Substance (BDS). The vaccine Drug Product is a solution for injection manufactured by aseptic addition of the BDS to the Drug Product Stabilizer Solution, which contains 2.5 mg/mL rice derived recombinant human serum albumin (rHSA) and 10 mM Tris buffer. This vaccine contains a trace amount of rice protein. The vaccine must be transported and stored frozen at -80°C to -60ºC.

The vaccine is currently approved for active immunisation of individuals 18 years of age or older to protect against EVD caused by ZEBOV. The MAH is claiming an extension of indication to include the

paediatric population from 1 year to less than 18 years of age. The proposed posology in children is the same as in adults, 1 mL of ≥72 million plaque forming units (pfu) administered as a solution for injection through intramuscular administration.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The EMA decision (P/0095/2017) regarding the agreement of a PIP, the granting of a deferral, and the granting of a waiver for rVSVΔG-ZEBOV-GP (EMEA-001786-PIP01-15) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council was adopted in April 2017.

2.1.4. General comments on compliance with GCP

The MAH claimed that the clinical studies were conducted in a manner commensurate with the principles of Good Clinical Practice including Independent Ethics Committee review, informed consent, and the protection of human subjects participating in biomedical research.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

No new non-clinical studies have been conducted since 2019 that would change or impact the ERA. Two clinical trials were completed since ERA approval:

Study V920-016

This clinical study (also known as PREVAC) submitted to support this extension of indication application was designed and initiated by external partners in 2017 following the 2014 to 2016 outbreak in West Africa.

Shedding, but not viremia, was assessed in saliva samples from a subset of 60 children in V920-016 (refer to Clinical Safety section for more information about the estimate proportion of children with detectable V920 virus in saliva and quantification of V920 shed in saliva by children after each vaccination).

Study V920-018

This was an open-label trial implemented as Part B of the Phase 3 ring vaccination trial for V920 (Part A, V920-010) that was conducted in Guinea during the 2014 to 2016 Ebola outbreak. The purpose of this trial was to evaluate the immunogenicity and safety of V920 in vaccinated frontline workers 18 years of age and older. Safety was assessed for all vaccinated subjects from Days 1 through 85 postvaccination and a subset of subjects from Days 1 through 180 postvaccination.

Shedding and viremia were not assessed in V920-018.

2.2.2. Discussion on non-clinical aspects

From these studies, the MAH concluded that shedding would not contribute to the environmental spread of V920, and therefore, risk to humans and the environment from exposure to the vaccine is expected to be negligible.

The MAH's statement on environmental spread cannot be supported as the high-level description of data obtained with study V920-016 indicate that shedding is occurring. Therefore, the dissemination of V920 in the human population from the vaccinees cannot be ruled out.

Risk management measures as described in the label should further limit exposure to V920 to the full extent possible. As a precaution vaccinees should attempt to avoid exposure of livestock to blood and bodily fluids for at least 6 weeks following vaccination to avoid the theoretical risk of spread of the rVSVΔG-ZEBOV-GP vaccine virus. Individuals who develop vesicular rash after receiving the vaccine should cover the vesicles until they heal. These recommendations have not changed based on results of V920-016.

It is also important to consider that shedding of V920 does not necessarily involve a risk. Shedding is a mechanism by which adverse effects for close contacts or the environment may occur depending on the stability of shed viral particles under environmental conditions outside the host, the route of transmission (e.g., spreading through aerosols, fecal-oral route of transmission via direct contact or contaminated fluids, vector-borne transmission, through parenteral exposure), the capacity to infect cells of other persons or animals and, as a last element in the chain of events for environmental risk to occur, the pathogenicity of the vaccine virus in the novel host organism (see Clinical Safety section for more information).

The MAH improved the ERA addendum by providing more detailed information and implemented additional clarifications to have a critical appraisal of the viral shedding results and modified relevant sections in the SmPC with clear instructions for parents and caregivers caring for recent young vaccinees.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of recombinant vesicular stomatitis virus - Zaire ebolavirus vaccine (live).

Considering the above data, recombinant vesicular stomatitis virus - Zaire ebolavirus vaccine (live) should be used according to the precautions stated in the SmPC to minimise any potential risks to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

Table 1: Tabular overview of clinical studies (V920-016 Protocol version 4.0)

Country/ Region	Study Title	Study Design	Dosing Regimen	Study Population	Participant Exposure	Key Endpoints
Guinea, Liberia, Mali, Sierra Leone	Partnership for Research on Ebola VACcination (PREVAC) A randomised, double-blind, placebo-controlled study of three vaccine strategies: Ad26.ZEBOV/MVA-BN-Filo vaccine, V920 with or without a boost at 56 days	Double-blind, placebo-controlled Participants were randomized to the following 5 groups in a 2:1:2:1:1 allocation: 1) Ad26.ZEBOV/MVA-BN-Filo (Ad26.ZEBOV [0.5 mL] followed by MVA-BN-Filo [0.5 mL] at Day 56) 2) Ad26.ZEBOV/MVA-BN-Filo matching placebo (placebo [0.5 mL] followed by placebo [0.5 mL] at Day 56) 3) 1-dose V920 (V920 [1.0 mL] followed by placebo [1.0 mL] at Day 56) 4) 2-dose V920 (V920 [1.0 mL] followed by V920 [1.0 mL] at Day 56) 5) V920 matching placebo (placebo [1.0 mL] followed by placebo [1.0 mL] at Day 56).	Single dose 1.0 mL V920 on Day 0 Single dose of 1.0 mL V920 or placebo at Day 56	Healthy male and female participants 1 year of age or older to protect against Ebola virus disease caused by *Zaire ebolavirus* Overall Population (all ages): Gender: Male: n=1094 Female: n=908 Median Age: 18.0 years Children (1 to 17 years of age): Gender: Male: n=546 Female: n=452 Median age: 8.0 years Adult Participants (>18 years of age): Gender: Male: n=548 Female: n=456 Median age: 27.0 years	Overall Population (all ages): Pooled V920: n=1201 • V920 1 dose: n=802 • V920 2 dose: n=399 Placebo: n=801 Children (1 to 17 years of age): Pooled V920: n=609 • V920 1 dose: n=407 • V920 2 dose: n=202 Placebo: n=389 Adults (≥18 years of age): Pooled V920: n=592 • V920 1 dose: n=395 • V920 2 dose: n=197 Placebo: n=412	Immunogenicity: • GP-ELISA (primary) and PRNT at baseline and Day 28, Month 3, and Month 12 after first vaccination Safety: • Solicited injection-site AEs and solicited systemic AEs of any grade severity, and Grade 3 or 4 unsolicited AEs after first vaccination and through Days 7, 14, and 28 after first vaccination • Solicited injection-site AEs and solicited systemic AEs of any grade severity, and Grade 3 or 4 unsolicited AEs after second vaccination, through Day 7 after second vaccination, and through Month 1 after second vaccination • SAEs through Month 12

A single phase 2 clinical trial V920-016 (PREVAC) was included in the application in support to the extension of indication to the paediatric population. No efficacy study was conducted in the new targeted population. Enrollment in the V920-016 study included V920 and Ad26.ZEBOV/MVA-BN-Filo vaccine arms with matched placebos.

2.3.2. Pharmacokinetics

Since the V920 vaccine contains a genetically modified organism, assessment of the risks to human health and to the environment was required. The main characteristics of the *in vivo* behaviour of the live V920 vaccine were previously evaluated through the assessment of vaccine viremia and shedding in adults at the initial marketing authorisation application.

Viral shedding/secondary transmission to close contacts, particularly immunocompromised hosts is listed as an important potential risk in the RMP to be addressed in the clinical studies V920-015 and V920-016 as an additional pharmacovigilance activity.

Another clinical study (EBOLAPED - NCT05130398) that aims to assess the clinical significance of shedding of rVSV RNA following vaccination with the V920 in children is also ongoing in Gabon.

In the V920-016 study, shedding in saliva of V920 was evaluated in a single-site (Redemption Hospital, Liberia) substudy to estimate the proportion of children with detectable V920 virus in saliva by qRT-PCR and to quantify V920 shed in saliva by children after each vaccination.

Vaccine shedding was assessed using a qRT-PCR developed to specifically detect and quantitate the rVSVΔG-ZEBOV-GP in human urine, plasma, swabs, skin, and synovial fluid. The assay primer set and probes target the junction of the VSV and ZEBOV-GP sequences in the vaccine such that this assay was specific for the V920 vaccine and did not detect wild-type VSV or ZEBOV. The assay consisted of extraction of RNA from clinical specimens using the Roche MagNa Pure 96 total nucleic acid isolation kit; one-step reverse transcription of mRNA to complementary DNA followed by amplification and detection of rVSVΔG-ZEBOV on the ABI QuantStudio 6. Results were reported as copies/mL using an external standard curve of rVSVΔG-ZEBOV-GP calibrators. To verify RNA extraction from the specimen and successful RT-PCR amplification, an internal control (MS2 RNA phage) was spiked into each sample prior

to RNA extraction and was amplified in parallel with the rVSVΔG-ZEBOV-GP target with each specimen for the entire assay procedure. The saliva matrix is currently being qualified in support of V920-016.

The sample size and results of the saliva shedding substudy are addressed in Clinical Safety section.

2.3.3. Pharmacodynamics

Humoral immune responses induced by V920 in adults and children were investigated in the V920-016 study. Cell mediated immune responses were investigated in a single site substudy (only in adults) and results of this substudy were not submitted by the MAH. Please refer to the Clinical Immunogenicity section for further details on immunogenicity assessment.

Mechanism of action

V920 consists of a live, attenuated recombinant vesicular stomatitis virus-based vector expressing the envelope glycoprotein gene of Zaire Ebola virus (rVSVΔG-ZEBOV-GP). Protective immunity against EBOV is not well understood. EBOV GP is the major antigen in the vaccine and has been shown to induce virus-neutralising antibodies as well as non-neutralising antibodies.

There is currently no established immunological correlate of protection against ZEBOV. The relative contributions of innate, humoral and cell-mediated immunity to protection from ZEBOV are unknown.

2.3.4. Discussion on clinical pharmacology

At the time of marketing authorisation, V920 shedding was observed in urine and saliva samples (respectively from Day 1 through Day 7 in urine and from Day 1 through Day 14 in saliva). V920 shedding was detected in a higher proportion of school-age children and adolescents (n=39, V920-007 study) compared to adults in general (all studies). At Day 7, V920 RNA was detectable in saliva in 35% of school-age children and in 88% of adolescents, and in a urine sample from 1 school-age child. Although, shedding in urine could have been investigated for better characterisation, evaluation of shedding only in saliva sample is deemed acceptable, as being the more relevant one based on the limited data available.

A limitation of this shedding substudy is that it did not include vaccinated adults. Including also the adult population would have allowed to compare proportions of shedding and levels of detected vaccine virus in paediatric and adult populations in a single study, with the same qualified analytical methods.

The qRT-PCR method used for the shedding substudy is comparable to the one applied at time of marketing authorisation and deemed acceptable. The MAH provided the LLOD and LLOQ values of the qualified assay to detect and measure rVSVΔG-ZEBOV-GP vaccine virus in human saliva specimens, which are respectively 100 copies/mL and 200 copies/mL.

As already discussed at the time of marketing authorisation, qRT-PCR cannot distinguish between live virus/vector and degraded virus/vector. It therefore remains difficult to define the risks associated to shedding based on qRT-PCR results.

The selected saliva sampling time-points after the first vaccination are considered acceptable, additional time-points should have been tested after the second vaccination to exclude delayed shedding in the participants randomised to 2 doses of V920.

The data submitted (proportion of tested participants with shedding > 0 and quantitative data submitted in this second round) are summarized and assessed in the Clinical Safety section.

2.3.5. Conclusions on clinical pharmacology

The characteristics of the *in vivo* behaviour of the live V920 vaccine were evaluated in children and adolescents through the assessment of vaccine shedding in a single site substudy (refer to the Clinical Safety section for further details).

Humoral immune responses induced by V920 in adults and children were investigated in the V920-016 study. Cell mediated immune responses were investigated in a single site substudy (only in adults) and results of this substudy were not submitted by the MAH. There are no established immunological correlates of protection (ICP) against EVD (refer to the Clinical Immunogenicity for further details).

2.4. Clinical immunogenicity

2.4.1. Dose response studies

No dose response studies were conducted in the paediatric population to support the requested extension of the approved therapeutic indication of Ervebo to include the paediatric population aged ≥1 year.

2.4.2. Main study – PREVAC (V920-016)

The study was designed to evaluate immunogenicity and safety in healthy children and adolescents from 1 to 17 years of age and adults 18 years of age and older.

The three vaccine strategies studied were:

- a single dose of V920 (i.e., approved regimen for active immunisation in individuals ≥18 year of age)
- two doses of V920 administered with 56 days interval
- the 2-dose heterologous vaccination regimen Ad26.ZEBOV/MVA-BN-Filo administered with 56 days interval (i.e., approved regimen for active immunisation in individuals ≥1 year of age)

A single site substudy was also conducted to estimate the proportion of children who shed vaccine virus in saliva after each vaccination.

The base study for V920-016 was a 12-month period after randomisation (first vaccination) for the assessment of primary and secondary safety and immunogenicity objectives. Enrolment and 12-month safety follow-up in the base study were complete. The CSR summarizes results from the base study. No data for participants who received Ad26.ZEBOV/MVA-BN-Filo were submitted.

All participants will be followed-up annually through 60 months (ongoing as per protocol version 5.0) to evaluate the durability of immune response and SAE.

Methods

Trial design

The original study protocol (version 1.0, 8-Oct-2016) was amended four times. In the initial study design, a total of 4,900 participants (3,500 adults and 1,400 children) were to be randomly allocated to one of the three vaccine strategies or placebo. The study size was powered to assess immune responses and safety outcomes separately in adults and children. However, protocol version 1.0 was never implemented,

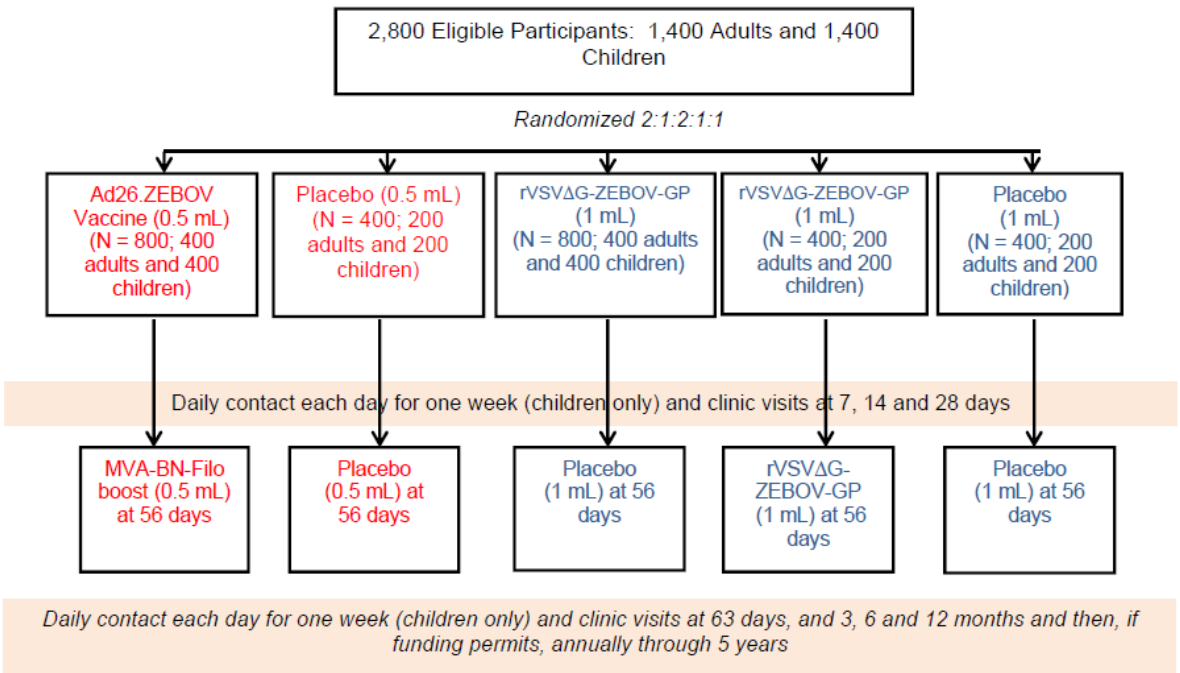
as the protocol was amended to begin the study with randomisation to the Ad26.ZEBOV/MVA-BN-Filo or matching placebo arm only (protocol version 2.0, 27-Feb-2017).

Under amended protocol version 3.0 (5-May-2017), randomisation to the two different V920 arms and V920-matching placebo was open. As the release potency of the V920 lot was higher, the sponsors decided to proceed with enrolment using a dilution of V920. Therefore, participants in the 1-dose V920 group and 2-dose V920 group were administered 1.0 mL of 2-fold diluted V920 corresponding to a potency level of approximately 5.0E7 pfu/mL. Enrolment of children was staged by age group. Children from 12 to 17 years of age were enrolled first (along with participants ≥18 years of age) and upon review of safety data and agreement by the DSMB, children 5 to 11 years of age were enrolled. Children 1 to 4 years of age were enrolled after review of prior safety in the older 2 age groups and agreement by the DSMB. No changes were made to the data collection plan.

Based on the safety experience with 2-fold diluted V920 considered acceptable by the DSMB for the children enrolled under protocol version 3.0 in the 3 age subgroups (1–4, 5–11, and 12–17 years), the protocol was amended to version 4.0 (15-Mar-2018):

- The dose of V920 was changed from the diluted dose level to the licensed dose of V920 (1.3E8 pfu/mL, with the geometric mean of available assay results of 9.4E7 pfu/mL).
- The target adult enrolment was reduced from 3,500 to 1,400.
- The target sample size for the saliva substudy was changed to 140 children (protocol versions 3.0 and 4.0) with approximately equal distribution of children in each of the 3 child age groups.
- The protocol and SAP were amended to state that the primary objectives would be accomplished with participants enrolled under version 4.0. Participants enrolled under version 3.0 would provide information on the safety and immunogenicity of diluted V920 compared with placebo for adults and children in each of the three age groups.

Figure 1: PREVAC study design – Protocol version 4.0



Finally, the protocol was amended (version 5.0, 3-Oct-2019) to add a long-term follow-up period consisting of annual visits for an additional 4 years after the Month 12 visit, which was instituted for all

participants. The secondary and exploratory objectives were updated accordingly. Data from this long-term follow-up period are not included in the CSR and will be summarised in a future report.

Study participants

Inclusion criteria

- Informed consent/assent
- Age 1 year and older
- Planned residency in the area of the study site for the next 12 months
- Willingness to comply with the protocol requirements

Exclusion criteria

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

Geographical region

1. Guinea at two sites (Landreah, an urban area in Conakry and Maferinyah, a rural area in the Forecariah region)
2. Liberia (Redemption Hospital in Monrovia)
3. Mali at two sites (Centre for Vaccine Development and the University Clinical Research Center, both in the capital Bamako),
4. Sierra Leone (Mambolo, a rural community in Kambia District, northern Sierra Leone).

Treatments

The study interventions were administered via intramuscular injection using a 3 mL syringe with a sterile needle in the upper, outer aspect of the arm (deltoid region). Children could alternatively be vaccinated in the thigh. The location of vaccination was recorded on the CRF.

Subjects were randomised to 5 different study interventions in a 2:1:2:1:1 allocation.

Table 2 Study interventions

Group Name	Intervention Regimen	Route of Administration	Use
Ad26.ZEBOV/ MVA-BN-Filo	Ad26.ZEBOV (0.5 mL) on Day 0 MVA-BN-Filo (0.5 mL) on Day 56	IM	Investigational vaccine
Placebo (0.5 mL)	Placebo (0.5 mL) on Days 0 and 56	IM	Placebo comparator
V920 (1 dose)	V920 (1.0 mL) on Day 0 Placebo (1.0 mL) on Day 56	IM	Investigational vaccine
V920 (2 dose)	V920 (1.0 mL) on Days 0 and 56	IM	Investigational vaccine
Placebo (1.0 mL)	Placebo (1.0 mL) on Days 0 and 56	IM	Placebo comparator

V920 was provided by the MAH and placebo (sterile normal saline [sodium chloride 0.9% for injection, United States Pharmacopeia, preservative free]) was provided by the study sponsors.

Two different V920 lots were used in study V920-016:

- WL00063635: participants randomised under protocol version 3.0 in Guinea Country and Liberia received 1.0 mL of 2-fold diluted V920, corresponding to a final potency of approximately 5.0E7 pfu/mL. Participants randomised under protocol version 4.0 in Liberia received 1.0 mL of undiluted V920, corresponding to a final potency of approximately 1.3E8 pfu/mL.

- WL00067929: participants randomised under protocol version 4.0 in Guinea Country, Mali and Sierra Leone received 1.0 mL of undiluted V920, corresponding to a final potency of approximately 3.0E8 pfu/mL.

Objectives

The primary and secondary objectives as established by the MAH are listed hereafter:

The primary objectives

In children from 1 to 17 years of age:

- To demonstrate that V920 (pooled V920 group – participants randomised both to the V920 1-dose and V920 2-dose arms) is superior to placebo (1.0-mL group) for the antibody response (GP-ELISA GMT) on Day 28 after randomisation (first vaccination)
- To demonstrate that V920 (2-dose group) is superior to placebo (1.0-mL group) for the antibody response (GP-ELISA GMT) at Month 12 after randomisation (first vaccination)
- To demonstrate that V920 (1-dose group) is superior to placebo (1.0-mL group) for the antibody response (GP-ELISA GMT) at Month 12 after randomisation (first vaccination).

In children versus adults:

- To demonstrate that V920 (pooled V920 group) is non-inferior (NI) in children 1 to 17 years of age compared with adults for antibody response (GP-ELISA GMT) on Day 28 after randomisation (first vaccination) – (with a non-inferiority test using a margin of 0.67.

The secondary objectives:

In children versus adults:

- To demonstrate that V920 (pooled V920 group) is non-inferior in children 3 to 17 years of age compared with adults for antibody response (GP-ELISA GMT) on Day 28 after randomisation (first vaccination)
- To demonstrate that V920 (pooled V920 group) is non-inferior in children 1 to 17 years of age compared with adults for antibody response (GP-ELISA GMT) on Day 28 after randomisation (first vaccination) – (with a non-inferiority test using a margin of 0.67)
- To summarize the percent difference for ELISA seroresponse (≥2-fold increase from baseline and ≥200 EU/mL, and ≥4-fold increase from baseline) between adults and children at Day 28 with the associated 95% CI.

In children and adults:

- To summarise V920 (separate and pooled V920 groups) and placebo (1.0-mL group) antibody response profiles (GP-ELISA and PRNT) at baseline, Day 28, Month 3, and Month 12 after randomisation (first vaccination)
- To determine the safety and tolerability of V920 through 1-year post-vaccination
- To summarise V920 (separate and pooled V920 groups) and pooled placebo (0.5- and 1.0-mL groups) SAEs (including death) before Day 56
- To summarise V920 (separate and pooled V920 groups) and pooled placebo (0.5- and 1.0-mL groups) SAEs (including death) from Day 56 to Month 12
- To summarise V920 (separate and pooled V920 groups) and pooled placebo (0.5- and 1.0-mL groups) SAEs (including death) from Day 1 to Month 12
- To summarise V920 (separate and pooled V920 groups) and pooled placebo (0.5- and 1-mL groups) injection-site reactions and targeted symptoms (solicited AEs, including joint events), at the vaccination visit, and on Days 7, 14, and 28 after randomisation (first vaccination) (including daily contacts for children only)
- To summarise V920 (separate and pooled V920 groups) and pooled placebo (0.5- and 1.0-mL groups) injection-site reactions and targeted symptoms (solicited AEs, including joint events), at the vaccination visit and on Day 7 and Month 1 after the second vaccination (including daily contacts for children only)
- To summarise V920 (separate and pooled V920 groups) and pooled placebo (0.5- and 1.0-mL groups) unsolicited AEs.

In children only:

- To summarise V920 (separate and pooled V920 groups) and pooled placebo (0.5- and 1.0-mL groups) changes from baseline in biochemical markers and CBC measurements by clinical significance (if available) on Days 7 and 63 after randomisation (first vaccination)
- In a subsample of children, to summarize V920 (separate and pooled V920 groups) and placebo (1.0-mL group) for shedding in saliva of VSV-ZEBOV at Days 7, 14, 28, 56, 63, and Month 3.

Outcomes/endpoints

Primary endpoints:

- Ebola virus glycoprotein (GP-EBOV) antibody response at Day 28 after randomisation (first vaccination), as measured by GP-ELISA

- GP-EBOV antibody response at Month 12 after randomisation (first vaccination), as measured by GP-ELISA.

Main secondary endpoints:

- GP-EBOV antibody response at Day 28, Month 3, and Month 12 after randomisation (first vaccination) as measured by GP-ELISA
- Neutralizing antibody response at Day 28, Month 3, and Month 12 after randomisation (first vaccination), as measured by PRNT
- SAEs, including death, occurring through Month 12
- Injection-site reactions and targeted symptoms of any grade severity and Grade 3 or 4 unsolicited AEs after first vaccination and through 7, 14, and 28 days after first vaccination
- Injection-site reactions and targeted symptoms of any grade severity and Grade 3 or 4 unsolicited AEs after second vaccination, through 7 days after second vaccination (63 days after first vaccination), and through approximately 28 to 35 days after second vaccination (Month 3 after first vaccination).

Other secondary safety endpoints:

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

Immunogenicity assessment

Blood sampling in adults and children for immunogenicity testing and future research were planned at baseline, at Day 7, 14, 28, 56, 63, and at Months 3, 6, 12, 24, 36, 48, 60.

Immunogenicity data was obtained using validated GP-ELISA and PRNT for specimens sampled at baseline, Day 28, Month 3, and Month 12 after randomisation (initial vaccination) in subjects that received one dose of V920, two doses of V920, or 1.0 mL placebo. Validated immunogenicity data were not obtained for the 0.5 mL placebo.

Serum samples were gamma irradiated to inactivate EBOV that may have been present before they were tested at laboratory. Gamma irradiation has been shown to result in an approximately 20% elevation in measured antibody response for negative clinical specimens and an approximately 20% reduction in postvaccination antibody response (1.21-fold decrease [95% CI = 1.15, 1.27-fold]) in the GP-ELISA. The effect of gamma irradiation on PRNT showed a similar reduction in postvaccination PRNT (1.19-fold decrease [95% CI = 1.06, 1.34-fold decrease]) without the elevation in measured antibody response for negative clinical samples. The effect of gamma-irradiation was discussed during the initial MAA procedure: "elevation in baseline and reduction in post-vaccination concentrations measured by GP ELISA (EU/ml) as a consequence of gamma-irradiation might result in a reduced estimation of the percentage of subjects achieving a 4-fold rise in response to vaccination".

GP-ELISA testing was conducted on all samples, whereas PRNT testing was conducted on samples from a randomly selected 50% subgroup of participants.

ZEBOV Anti-GP IgG Human ELISA

To measure and quantify total IgG antibodies against V920, an indirect ELISA which utilizes a purified recombinant Ebola Zaire glycoprotein (rGP) as the coating antigen was 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 ELISA units/mL (EU/mL). The assay was qualified and validated, and assessed at initial MAA and deemed acceptable.

One half of LLOQ was used when a sample result was below LLOQ (36.11 EU/mL).

rVSVΔG -ZEBOV-GP $PRNT_{60}$

A $PRNT_{60}$ was validated to determine the neutralizing antibody levels in human sera following the administration of V920. In this assay, serum was diluted from 1:5 to 1:10240 and mixed with an equal volume of diluted V920 for final dilutions of 1:10 to 1:20480. 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. Determination of the $PRNT_{60}$ was based upon the percent reduction in viral plaques in the presence of serum compared to that of the virus control without serum. The $PRNT_{60}$ assay was qualified and validated, and assessed concluding that the assay was suitable for its intended use.

One half of LLOQ was used when a sample result was below LLOQ ($PRNT_{60}$ 35).

Sample size

In the protocol version 1.0, sample size was established to provide power to compare safety and immunogenicity separately for adults (N=3,500) and children (N=1,400). Among these participants, 1,000 adults and 400 children were to be respectively randomised to the V920 (1 dose) or the Ad26.ZEBOV/MVA-BN-Filo interventions; and 500 adults and 200 children were to be respectively randomised to the V920 (2 dose) or placebo (0.5 mL) or placebo (1.0 mL) interventions.

The minimum number of paediatric subjects was approximately 1,000 based on a conservative projection of approximately 20% unevaluable data (e.g., dropout, missing samples, etc.) in studies conducted by sponsors other than the MAH.

The planned sample size was greater than what required to address the primary objectives and in order to permit the exploration of subgroups and preserve power in the event there were more participants with elevated antibodies at baseline than anticipated.

In protocol version 4.0, sample size was modified for the adult population from N=3,500 to N=1,400. The planned size for the paediatric population was not modified. The power was maintained. The multiplicity adjusted power for the primary hypotheses is at least 96% (0.99*0.99*0.99*0.99). For safety, the sample sizes allow at least 99% power to detect a 4% difference between V920 and placebo (5% vs 1%).

For the saliva shedding substudy, the planned sample-size was of approximately 140 children in each of versions 3.0 and 4.0 (280 in total). For both versions, efforts were to be made to enrol 1/3 of the total number of children in each age group (i.e., 1-4, 5-11, and 12-17 years).

Randomisation and blinding (masking)

Randomisation for V920 followed a 1:2:1:1 ratio (Ad26.ZEBOV/MVA-BN-Filo matching placebo (0.5 mL): V920 (1-dose): V920 (2 dose): V920 matching placebo (1.0 mL)) under protocol version 3.0 and 4.0.

Syringes were pre-labelled with a unique SID number according to a centrally prepared randomisation schedule. The tear-off label also included a bar code identifier. For each vaccination centre, the randomisation schedule was prepared using block randomisation to ensure the desired allocation ratio for the five arms of the study for each vaccination centre.

The person administering the vaccination could be able to differentiate syringes by the fill volume, which was respectively 1.0 mL for V920 and matching placebo or 0.5 mL for Ad26.ZEBOV/MVA-BN-Filo and matching placebo. However, vaccinators could not be aware whether the assignment was to active vaccine or placebo.

At the time of vaccination, a tear-off label on the syringe that included the SID was to be attached to the baseline CRF. This was the primary link used between the vaccine administered and the PID, and PIDs associated with SIDs were to be available to the pharmacy. The syringe used at 56 days was to be labelled with the volunteer's PID.

With this approach, randomisation did not occur until the participant was vaccinated with the prime vaccine.

Study participants and clinical staff assessing the study participants for safety and laboratory outcomes had to be fully blinded until all participants completed 12 months of follow-up. The laboratories carrying out the safety and immunogenicity analyses were to be blinded to the vaccine assignment.

The study was unblinded after 12-month follow-up visits were completed for all participants.

Statistical methods

Analysis populations

- *Per-Protocol population (PP)* was used as the primary population for the analysis of immunogenicity data in this study. The PP population consisted of all randomised and vaccinated subjects who meet the inclusion criteria, did not meet exclusion criteria, and did not have major protocol deviations. Subjects who were seronegative (baseline ELISA <200 EU/mL) and seropositive (baseline ELISA ≥200 EU/mL) were included in the PP population.

- *Full Analysis Set (FAS)* was the secondary population for the analysis of immunogenicity data in this study. The FAS population consisted of all randomised and vaccinated subjects with serology data according to the treatment they actually received. The FAS was used if the difference in the number of subjects between the PP and FAS was ≥10%.

PRNT testing was only done on a 50% randomised subgroup of samples (N=approximately 1214). The subgroup had to consist of 100% samples from children aged 1-17. The remainder had to consist of a random sample of adults. Adjustments to this strategy were made to accommodate actual enrolment and ensure approximately 300 adult samples. To perform the PRNT selection, after enrolment completed, the study sponsor provided the MAH a blinded allocation list of all V920 and 1 mL placebo subjects. Additional variables included protocol amendment version 3.0 or 4.0, age, and number of aliquots at baseline.

- *All Subjects as Treated (ASaT)* was used for the analysis of safety data in this study. The ASaT population consisted of all randomised subjects who received at least one dose of study vaccination and had follow-up of least one timepoint.

Subjects who did not receive 1 of the 5 treatments were excluded from all analyses.

Statistical methods for key immunogenicity analyses

Analysis of antibody titers for the primary and secondary hypotheses were conducted by log-transforming the data, performing analysis of variance (ANOVA) on the log-transformed data, model, and un-transforming the statistics. The ANOVA model included treatment group as a covariate.

For multiplicity, a fixed sequence test was used to test the 5 immunogenicity hypotheses to control the overall type 1 error rate at a 1-sided α=0.025.

The following immunogenicity summaries were provided:

- Means and 95% CIs of the GMT and GMFI from baseline
- Counts, percentages, and 95% CIs of the proportion of subjects who achieve a:
  - Seroresponse at any time during study and for each timepoint defined as:
    - ELISA: Primary: ≥2-fold increase from baseline and ≥200 EU/mL; Secondary: ≥4-fold increase from baseline
    - PRNT: ≥4-fold increase from baseline

GMT and GMFI summaries were based on ANOVA on log-transformed data and exponentiating the summary statistics. The ANOVA model included treatment group as a covariate.

Seroresponse summaries were based on frequencies and exact 95% CIs. The V920 groups were summarised separately and pooled.

The estimate of the percent difference for the 2 definitions of ELISA seroresponse between adults and children at Day 28 with the associated Miettinen and Nurminen 95% CI had to be provided.

Formal superiority and non-inferiority hypotheses were tested for children, and for children compared to adults, for key primary and secondary objectives. For the superiority objectives, rejecting the null hypothesis required the lower bound of the two-sided 95% CI of the GP-ELISA V920 / Placebo GMT ratio to be greater than 1.

For the NI primary objective, rejecting the null hypothesis required that the lower bound (LB) of the 95% CI for the ratio of the GMT in children 1 to 17 years of age / GMT in adults was greater than 0.5 for the antibody response (GP-ELISA GMT) on Day 28 after randomisation (initial vaccination). For the NI secondary objectives, the LB of the 95% CI for the NI hypotheses had to be greater than 0.67.

Formal superiority and non-inferiority hypotheses are considered appropriate.

Analysis of immunogenicity endpoints

Please refer to section immunogenicity assessment.

Demographic and baseline characteristics, subgroup analyses and effect of baseline factors

Demographic variables (e.g., age, sex, race/ethnicity, protocol version), baseline characteristics, and prior and concomitant therapies/vaccinations were summarized by treatment either by descriptive statistics or categorical tables.

Subgroup included age, gender, HIV status, baseline seronegativity and seropositivity (baseline ELISA <200 EU/mL and baseline ELISA ≥200 EU/mL) and protocol version. The age groups were defined <3, 3 to 11, 12 to 17 and adults.

Subgroup analyses for protocol version 3.0 versus 4.0 could be done for selected analyses. All immunogenicity endpoints were summarised by subgroups.

Results

Participant flow

The study results focused on the protocol version 4.0 population (licensed dose of V920). Analysis tables for the protocol version 3.0 population and the combined protocol version 3.0 and 4.0 population were also presented in the CSR.

A total of 3,036 participants were randomised to the V920 and placebo groups across 6 study sites in 4 countries.

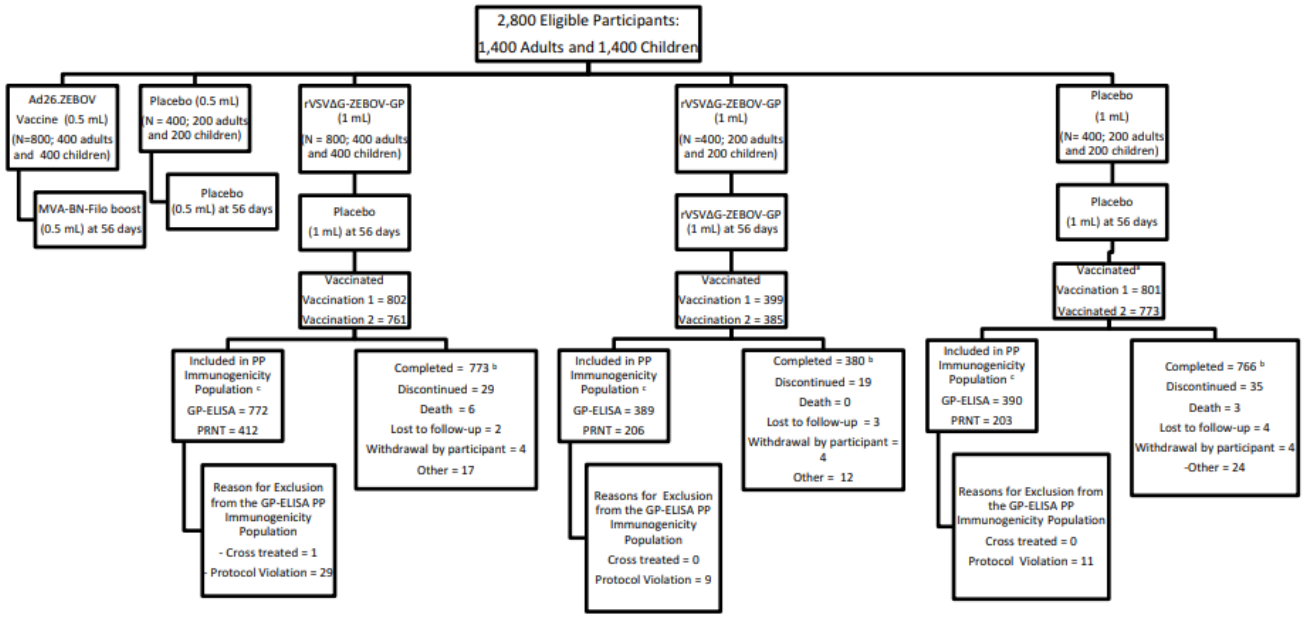
Under protocol version 4.0, a total of 2,002 participants (998 children, 1,004 adults) were randomised to the V920 and placebo groups and 1,919 participants (95.9%) received both vaccinations to which they were randomised and completed the study. A majority of participants was recruited in Guinea (approximately 35% equally distributed between the two sites), 25% were recruited in Sierra Leone, 22% in Mali (equally distributed between the two sites) and 17% recruited in Liberia. A total of 1,551 participants were included in the PP Immunogenicity Population for GP-ELISA and a total of 821 participants were included in the PP Immunogenicity Population for PRNT.

Among the 998 children, 40.8% (n=407) were randomised to V920 (1 dose), 20.2% (n=202) were randomised to V920 (2 dose), 39.0% (n=389) were randomised to placebo (0.5 and 1.0 mL), and 96.6% (n=964) completed the study.

Among the 1,004 adults, 39.34% (n=395) were randomised to V920 (1 dose), 19.62% (n=197) were randomised to V920 (2 dose), 41.04% (n=412) were randomised to placebo (0.5 and 1.0 mL), and 95.1% (n=955) completed the study.

Among the paediatric participants contributing to the primary GP-ELISA analysis and vaccinated with 1 dose of V920, 52 were aged 1 to <3 years of age, 203 were aged 3 to <12, and 131 were aged 12 to <18. For the primary PRNT analysis, numbers of participants randomised to 1 dose V920 were respectively 40, 140 and 130 in the 3 age sub-categories. In addition, among children aged 1 to <3 years, there were respectively 22/52 aged 1 to <2 years and 30/52 aged 2 to <3 years contributing to GP-ELISA analysis and respectively 19/40 aged 1 to <2 years and 21/40 aged 2 to <3 years contributing to PRNT analysis.

Figure 2: V920-016 Participant disposition (Protocol version 4.0)



Row 1 and Row 2 represent planned study design sample sizes. Row 3 – Row 5 represent actual sample sizes.
[a] Placebo=0.5- and 1.0-mL placebo groups.
[b] Completed includes participants who completed at least 1 study vaccination and follow-up at Month 12
[c] PP Immunogenicity Population consisted of participants who did not violate the inclusion/exclusion criteria, had baseline serology data, received at least 1 dose of 1-dose V920, 2-dose V920, or 1.0-mL placebo (V920 matching placebo), and did not have important protocol deviations

Under Protocol version 3.0, a total of 1,034 participants (559 children, 475 adults) were randomised to the V920 and placebo groups and 1,021 participants (98.7%) received both vaccinations to which they were randomised and 1,001 (96.8%) completed the study. A majority of approximately 75% of participants were recruited in Guinea (equally distributed between the two sites). The MAH specified that eligibility for enrolment was assessed on a first-come, first-serve basis. Among the randomised paediatric participants, a total of 18 were aged 1 to >3 years, 246 were aged 3 to <12 years and 295 were aged 12 to <18 years.

Table 3: Disposition of participants (All Participants - Protocol version 3.0)

	V920 1 Dose		V920 2 Dose		Pooled V920[a]		Placebo[b]		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	414		207		621		413		1,034	
Vaccinated at										
Vaccination 1	414	(100.0)	207	(100.0)	621	(100.0)	413	(100.0)	1,034	(100.0)
Vaccination 2	407	(98.3)	206	(99.5)	613	(98.7)	408	(98.8)	1,021	(98.7)
Study Disposition										
Completed	399	(96.4)	201	(97.1)	600	(96.6)	401	(97.1)	1,001	(96.8)
Discontinued	15	(3.6)	6	(2.9)	21	(3.4)	12	(2.9)	33	(3.2)
Death	1	(0.2)	0	(0.0)	1	(0.2)	1	(0.2)	2	(0.2)
Lost To Follow-Up	2	(0.5)	1	(0.5)	3	(0.5)	3	(0.7)	6	(0.6)
Withdrawal By Subject	3	(0.7)	0	(0.0)	3	(0.5)	1	(0.2)	4	(0.4)
Other	9	(2.2)	5	(2.4)	14	(2.3)	7	(1.7)	21	(2.0)

[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=0.5- and 1.0-mL placebo groups.

Table 4: Participants randomised by investigator and vaccination Group (All participants randomised)

Location	Trial-Site	V920 1 Dose - Version 3, Diluted V920 (N=414)	V920 1 Dose - Version 4, Undiluted V920 (N=815)	V920 2 Dose - Version 3, Diluted V920 (N=206)	V920 2 Dose - Version 4, Undiluted V920 (N=385)	Placebo - Version 3, Diluted V920 (N=413)	Placebo - Version 4, Undiluted V920 (N=800)
Guinea Country		**304**	**287**	**152**	**141**	**305**	**285**
	V920-016-0001	166	163	83	80	165	161
	V920-016-0002	138	124	69	61	140	124
Liberia		**110**	**136**	**54**	**68**	**108**	**136**
	V920-016-0003	110	136	54	68	108	136
Mali		**0**	**180**	**0**	**85**	**0**	**177**
	V920-016-0005	0	88	0	40	0	86
	V920-016-0006	0	92	0	45	0	91
Sierra Leone		**0**	**212**	**0**	**91**	**0**	**202**
	V920-016-0004	0	212	0	91	0	202

Table 5: Summary of Nonconformities

	V920 1 Dose		V920 2 Dose		Pooled V920[a]		Placebo[b]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	1,216		606		1,822		1,214	
with one or more nonconformities	47	(3.9)	17	(2.8)	64	(3.5)	42	(3.5)
with no nonconformities	1,169	(96.1)	589	(97.2)	1,758	(96.5)	1,172	(96.5)
Participant nonconformity	**47**	**(3.9)**	**17**	**(2.8)**	**64**	**(3.5)**	**42**	**(3.5)**
ICF/ICF process	10	(0.8)	2	(0.3)	12	(0.7)	10	(0.8)
Involves a minor child	28	(2.3)	10	(1.7)	38	(2.1)	21	(1.7)
Meets the definition of an UP	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
Missing Initial ICF	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)
Other Deviation	30	(2.5)	13	(2.1)	43	(2.4)	25	(2.1)
Participant randomized but did not meet all eligibility criteria	1	(0.1)	0	(0.0)	1	(0.1)	2	(0.2)
Pregnancy test results not obtained prior to vaccine administration	0	(0.0)	1	(0.2)	1	(0.1)	0	(0.0)
Required labs not collected	9	(0.7)	2	(0.3)	11	(0.6)	5	(0.4)
Serious NC[c]	5	(0.4)	1	(0.2)	6	(0.3)	2	(0.2)

Every participant is counted a single time for each applicable row and column.
[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=0.5- and 1.0-mL placebo groups.
[c] As assessed by sponsor.
ICF=Informed Consent Form; NC=nonconformity; UP=unanticipated problem.

The category of "other deviation" included such deviations as the use of the wrong sampling kit (i.e., mixing up a minor child and adult sampling kit), the collection of an additional blood sample, failure to collect a sample (e.g., saliva), or insufficient blood volume collection, a missing laboratory test result, an abnormal test result that was not transmitted by the laboratory to the investigator, a failure to retest a Grade 3 laboratory test result, or use of the wrong normal range, an out-of-window visit, the administering of the wrong second vaccination, etc.

Recruitment

The following dates specified in the CSR are related to protocol version 3.0 and 4.0:

- First Participant, First Visit: 24-Jul-2017
- Last Participant, Last Visit (Data Cut-off): 24-Dec-2019
- Database Lock Date: 1-Nov-2021

The base study was a 12-month period after randomisation (first vaccination) for the assessment of primary and secondary safety and immunogenicity objectives. Enrolment and 12-month safety follow-up are complete. Annual follow-up of all participants through 60 months (protocol version 5.0) is ongoing.

Conduct of the study

Major amendments made to the protocol

The initial study protocol (version 1.0) was amended four times and the main changes are summarised in the Trial Design and Statistical Methods sections.

Post-hoc analyses

Since the dates of collection of a substantial number of samples were outside of the prespecified day ranges for the immunogenicity analyses in the SAP, post hoc analyses that removed restrictions for the prespecified day ranges at each immunogenicity analysis time point were conducted for key primary and secondary immunogenicity analyses for both GP-ELISA and PRNT.

Protocol compliance and GCP inspection findings

According to the MAH, investigative study sites were monitored to assess compliance with the study protocol and with GCP. Study data were reviewed for accuracy, completeness, and consistency and verified versus source documentation according to study SOPs and the Monitoring Plan.

An audit was conducted by a third party at 2 sites: site 102 in Guinea and site 304 in Sierra Leone. During the credential verification process at site 102, it was discovered that an investigator falsified her/his diploma. This investigator oversaw the signing of 35 ICFs, carried out 6 medical consultations, reported approximately 10 targeted symptoms, and oversaw 376 follow-up visits. A CAPA plan was implemented to manage impact and validate study activities, including the verification of the reconsents and other corrective actions performed at an on-site monitoring visit. Following the on-site monitoring visit, 1 of 35 consents was missing. The affected participant's data was not transferred from the sponsor to the MAH and was therefore excluded from all the analyses of the CSR.

Baseline data

Subject Characteristics

Under protocol version 4.0, a total of 2,002 participants (998 children, 1,004 adults) were randomised to the V920 (1 dose), V920 (2 dose), placebo (0.5 mL) and placebo (1.0 mL) interventions.

Among the 998 randomised children, 54.7% were male (n=546) and 45.3% were female (n=452), all were HIV negative. Median age was 8.0 years (range: 1 to 17 years), with 15.5% (n=155) aged 1 to <3 years, 51.6% (n=515) aged 3 to <12 years, and 32.9% (n=328) aged 12 to <18 years.

Table 6: Participant characteristics (All randomised participants – Protocol version 4.0 – Children)

	V920 1 Dose		V920 2 Dose		Pooled V920		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	407		202		609		389		998	
Sex										
Male	222	(54.5)	117	(57.9)	339	(55.7)	207	(53.2)	546	(54.7)
Female	185	(45.5)	85	(42.1)	270	(44.3)	182	(46.8)	452	(45.3)
Age (Years)										
<3	56	(13.8)	39	(19.3)	95	(15.6)	60	(15.4)	155	(15.5)
3 to 11	213	(52.3)	97	(48.0)	310	(50.9)	205	(52.7)	515	(51.6)
12 to 17	138	(33.9)	66	(32.7)	204	(33.5)	124	(31.9)	328	(32.9)
≥18	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Mean	8.6		8.2		8.4		8.3		8.4	
SD	4.9		5.1		5.0		5.0		5.0	
Median	9.0		8.0		9.0		8.0		8.0	
Range	1 to 17		1 to 17		1 to 17		1 to 17		1 to 17	

Under Protocol Version 4.0, participants <3 years of age were 88 males and 67 females (participants 1 to <2 years of age were 34 males and 30 females and participants ≥2 to <3 years of age were 54 males and 37 females), participants 3 to 11 years of age were 264 males and 251 females and participants 12 to 17 years of age were 194 males and 134 females.

Only a total of 155 children aged 1-3 years were enrolled under protocol version 4.0, with 56 randomised to the V920 (1 dose) intervention and 60 randomised to placebo (0.5 and 1.0 mL). The additional 39 children aged 1 to <3 years randomised to the V920 (2 dose) under protocol version 4.0 only contributed to the Day 28 objectives/endpoints and cannot support immunogenicity and safety assessment at Month 12 for this extension of indication application.

Overall, the following numbers of participants aged ≥1 to <3 years were randomised in the APaT population:

- Protocol Version 4.0: 64 randomised participants from 1 to <2 years of age (referred to as aged 1 year) and 91 participants from ≥2 to <3 years of age (referred to as aged 2 years). Among those aged 1 to <2 years, 25 were allocated to V920 (1 Dose), 16 to V920 2 Dose and 23 to placebo. Among those aged ≥2 to <3 years, 33 were allocated to V920 (1 Dose), 21 to V920 2 Dose and 37 to placebo.

- Protocol Version 3.0: 8 randomised participants from 1 to <2 years of age and 10 participants from ≥2 to <3 years of age. Among those aged 1 to <2 years, 2 were allocated to V920 (1 Dose), 2 to V920 2 Dose and 4 to placebo. Among those aged ≥2 to <3 years, 6 were allocated to V920 (1 Dose), none to V920 2 Dose and 4 to placebo.

Among the 1,004 randomised adults, 54.6% were male (n=548) and 45.4% were female (n=456) and 1.9% were HIV positive. Median age was 27.0 years (range: 18 to 76 years); with 98.2% (n=986) of adults between the ages of 18 and 65 years and only 1.8% (n=18) adults older than 65 years.

Table 7: Participant characteristics (All randomised participants – Protocol version 4.0 – Adults)

	V920 1 Dose		V920 2 Dose		Pooled V920		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	395		197		592		412		1,004	
Sex										
Male	213	(53.9)	110	(55.8)	323	(54.6)	225	(54.6)	548	(54.6)
Female	182	(46.1)	87	(44.2)	269	(45.4)	187	(45.4)	456	(45.4)
Age (Years)										
18 to 65	386	(97.7)	194	(98.5)	580	(98.0)	406	(98.5)	986	(98.2)
>65	9	(2.3)	3	(1.5)	12	(2.0)	6	(1.5)	18	(1.8)
Mean	31.1		29.7		30.6		30.8		30.7	
SD	13.0		11.8		12.6		12.6		12.6	
Median	27.0		26.0		26.5		27.0		27.0	
Range	18 to 74		18 to 72		18 to 74		18 to 76		18 to 76	
Race										
Missing	395	(100.0)	197	(100.0)	592	(100.0)	412	(100.0)	1,004	(100.0)
HIV Status										
Negative	382	(96.7)	195	(99.0)	577	(97.5)	408	(99.0)	985	(98.1)
Positive	13	(3.3)	2	(1.0)	15	(2.5)	4	(1.0)	19	(1.9)

Under protocol version 3.0, a total of 1034 participants (559 children, 475 adults) were randomised to the V920 (1 dose), V920 (2 dose), placebo (0.5 mL) and placebo (1.0 mL) interventions. Among these 53% were male (n=549) and 47% were female (n=485)

Paediatric participants <3 years of age were 7 males and 11 females (participants 1 to <2 years of age were 3 males and 5 female, participants ≥2 to <3 years of age were 4 males and 6 females), participants 3 to 11 years of age were 134 males and 112 females, and participants 12 to 17 years of age were 145 males and 150 females.

Table 8: Participants by age category and sex (All randomised participants)

	V920 1 Dose - Version 3, Diluted V920			V920 1 Dose - Version 4, Undiluted V920			V920 2 Dose - Version 3, Diluted V920			V920 2 Dose - Version 4, Undiluted V920			Placebo - Version 3, Diluted V920			Placebo - Version 4, Undiluted V920		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Participants in population	222	192	414	435	367	802	109	98	207	227	172	399	218	195	413	432	369	801
Age (Years)																		
<3	2	6	8	35	21	56	0	2	2	22	17	39	5	3	8	31	29	60
3 to 11	53	49	102	107	106	213	27	23	50	50	47	97	54	40	94	107	98	205
12 to 17	65	62	127	80	58	138	26	30	56	45	21	66	54	58	112	69	55	124
≥18	102	75	177	213	182	395	56	43	99	110	87	197	105	94	199	225	187	412
Mean	21.8	18.9	20.4	18.1	21.6	19.7	20.6	22.3	21.4	18.1	19.8	18.8	21.4	21.3	21.4	18.7	21.2	19.8
SD	15.5	12.8	14.3	12.8	16.9	14.9	13.2	16.1	14.6	13.2	15.2	14.1	15.5	13.1	14.4	13.4	16.3	14.8
Median	17.0	16.0	16.0	17.0	17.0	17.0	19.0	16.0	17.0	17.0	18.0	17.0	17.0	17.0	17.0	18.0	18.0	18.0
Range	2 to 78	1 to 66	1 to 78	1 to 74	1 to 71	1 to 74	3 to 74	1 to 62	1 to 74	1 to 68	1 to 72	1 to 72	1 to 74	1 to 65	1 to 74	1 to 76	1 to 75	1 to 76

Baseline serology

Of the 1,551 participants in the GP-ELISA PP population of protocol version 4.0:

- 321 (20.7%) were seropositive for GP-ELISA (defined as ≥200 EU/mL) at baseline
- 1,087 (70.1%) were seronegative for GP-ELISA (defined as <200 EU/mL)
- 143 (9.2%) had missing or unevaluable baseline serology samples/results.

Numbers analysed

Immunogenicity data for the V920 (1 dose), V920 (2 dose) and 1.0-mL placebo groups were obtained from samples tested in the validated GP-ELISA and PRNT at the central laboratory. Participants randomised to the 0.5 mL placebo were not included in the GP-ELISA PP Immunogenicity Population (but both 0.5 mL and 1.0 mL placebo arms were included in the safety endpoints).

GP-ELISA testing was conducted on all samples and overall, 1,551 out of 1,602 (96.8%) participants contributed to these analyses for the PP population of protocol version 4.0.

Table 9: Participant accounting for the GP-ELISA in the Per-Protocol immunogenicity population by vaccination group (All randomised or enrolled participants – Protocol version 4.0)

	V920 1 Dose (N= 802)	V920 2 Dose (N= 399)	Pooled V920[a] (N= 1201)	Placebo[b] (N= 401)	Total (N= 1602)
Participants Vaccinated	**802**	**399**	**1201**	**401**	**1602**
Reasons for Exclusion From the Per-Protocol Immunogenicity Population	**30**	**9**	**39**	**11**	**50**
Participants Excluded due to Cross Treatment	1	0	1	0	1
Protocol Violation	29	9	38	11	49
Included in Per-Protocol Immunogenicity Population for GP-ELISA (EU/ml)	**772**	**389**	**1161**	**390**	**1551**
Missing or out of day Range Serology Samples/Results at Each Time Point[c]					
Day 1 (Baseline)	42	20	62	23	85
Day 28	93	50	143	45	188
Month 3	39	17	56	23	79
Month 12	196	106	302	119	421
No Serology Data	0	1	1	0	1

[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=1.0-mL placebo group.
[c] Participants are counted once in each applicable exclusion category. A participant may appear in more than one category.
N=number of participants randomized to the respective intervention group.
GP-ELISA=glycoprotein enzyme-linked immunosorbent assay.

PRNT testing was conducted on samples from 631 children and on samples from 190 adult under protocol version 4.0. These numbers correspond to 63.2% of the children and 18.9% of the adults randomised to V920 or 1.0-mL placebo under protocol version 4.0. Overall, 731 participants had no serology data available for the PRNT analyses.

Table 10: Participant accounting for the PRNT in the Per-Protocol immunogenicity population by vaccination group (All randomised or enrolled participants – Protocol version 4.0)

	V920 1 Dose (N= 802)	V920 2 Dose (N= 399)	Pooled V920[a] (N= 1201)	Placebo[b] (N= 401)	Total (N= 1602)
Participants Vaccinated	**802**	**399**	**1201**	**401**	**1602**
Reasons for Exclusion From the Per-Protocol Immunogenicity Population	**30**	**9**	**39**	**11**	**50**
Participants Excluded due to Cross Treatment	1	0	1	0	1
Protocol Violation	29	9	38	11	49
Included in Per-Protocol Immunogenicity Population for PRNT	**412**	**206**	**618**	**203**	**821**
Missing or out of day Range Serology Samples/Results at Each Time Point[c]					
Day 1 (Baseline)	36	21	57	15	72
Day 28	48	31	79	43	122
Month 3	21	12	33	21	54
Month 12	123	72	195	70	265
No Serology Data	360	184	544	187	731

[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=1.0-mL placebo group.
[c] Participants are counted once in each applicable exclusion category. A participant may appear in more than one category.
N=number of participants randomized to the respective intervention group.
PRNT=plaque reduction neutralization test.

Children accounting for the GP-ELISA or PRNT in the Per-Protocol Immunogenicity Population by vaccination group (Protocol version 4.0):

- 1 to <2 years of age: 48 were included in GP-ELISA and 38 in PRNT. Among these, for GP ELISA, 22 were treated with V920 (1 Dose), 14 with V920 (2 Doses) and 12 with placebo. For PRNT, 19 were treated with V920 (1 Dose), 9 with V920 (2 Doses) and 10 with placebo.

- ≥2 to <3 years of age: 67 were included in GP-ELISA and 49 in PRNT. Among these, for GP ELISA, 30 were treated with V920 (1 Dose), 20 with V920 (2 Doses) and 17 with placebo. For PRNT, 21 were treated with V920 (1 Dose), 16 with V920 (2 Doses) and 12 with placebo.

- 3 to 11 years of age: 413 were included in GP-ELISA and 290 in PRNT. Among these, for GP ELISA, 203 were treated with V920 (1 Dose), 96 with V920 (2 Doses) and 114 with placebo. For PRNT, 140 were treated with V920 (1 Dose), 68 with V920 (2 Doses) and 82 with placebo.

- 12 to 17 years of age: 256 were included in GP-ELISA and 254 in PRNT. Among these, for GP ELISA, 131 were treated with V920 (1 Dose), 65 with V920 (2 Doses) and 60 with placebo. For PRNT, 130 were treated with V920 (1 Dose), 65 with V920 (2 Doses) and 59 with placebo.

This corresponds to a total PP GP ELISA paediatric population of 784 and a total PP PRNT paediatric population of 631. In addition, this corresponds to about 80% of PP GP ELISA population ≥1 to <2 years of age, about 75% of PP GP ELISA population ≥2 to <3 years, about 70% of PP GP ELISA population 3 to 11 years included in the PP PRNT population and almost 100% of PP GP ELISA population 12-17 years included in the PP PRNT population.

The MAH also provided the numbers of participants (adults and children) randomised for the PP population of protocol version 3.0 and protocol version 4.0 combined. Overall, 2,342 out of 2,430 vaccinated participants (96.4%) were included in the GP-ELISA PP Immunogenicity Population and 1,226 out of 2,430 vaccinated participants (50.4%) were included in the PRNT analyses under combined protocols.

It is estimated that under protocol version 3.0 respectively 791 participants were included in the GP-ELISA and 405 in PRNT PP Immunogenicity Populations.

Outcomes and estimation

Primary immunogenicity endpoints for superiority analyses

In children 1 to 17 years of age, the Day 28 GP-ELISA GMT for participants vaccinated with 1 dose or 2 doses of V920 (pooled V920) was superior to the placebo GMT (p<0.001). Superiority was met under protocol version 4.0 (Table 11) and when data combined from both protocol version 3.0 and 4.0 (Table 12) were analysed.

Table 11: Statistical analysis (Superiority) of pooled V920 vs. placebo in children based on Day 28 GP-ELISA Geometric Mean Titers (GP-ELISA Per-Protocol Immunogenicity Population - Protocol Version 4.0)

		Comparison Group A			Comparison Group B			Estimated Fold Difference Group A / Group B	p-value[b]	Type Specific Conclusion
Assay	Comparison Group A vs. Comparison Group B	N	n	Estimated GMT[a] (EU/mL)	N	n	Estimated GMT[a] (EU/mL)	(95% CI)		
GP-ELISA	Pooled V920[c] vs. Placebo[d]	546	499	1,748.8	186	173	96.4	18.15 (14.96, 22.01)	<0.001	Superiority is met
Overall conclusion: The superiority criteria were met.										

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.
[a] Based on an ANOVA model with a response of the natural log of individual titers and a fixed effect for intervention group.
[b] p-value for the comparison of the GMT ratio to the lower bound (1).
[c] Pooled V920=V920 1 dose or 2 dose.
[d] Placebo=1.0-mL placebo group.
N=number of participants with serology data at Day 28 according to the intervention to which they were randomized; n=number of participants contributing to the analysis.
CI=confidence interval; GMT=geometric mean titer; GP-ELISA=glycoprotein enzyme-linked immunosorbent assay.

Table 12: Statistical analysis (Superiority) of pooled V920 vs. placebo in children based on Day 28 GP-ELISA Geometric Mean Titers (GP-ELISA Per-Protocol Immunogenicity Population)

		Comparison Group A			Comparison Group B			Estimated Fold Difference Group A / Group B	p-value[b]	Type Specific Conclusion
Assay	Comparison Group A vs. Comparison Group B	N	n	Estimated GMT[a] (EU/mL)	N	n	Estimated GMT[a] (EU/mL)	(95% CI)		
GP-ELISA	Pooled V920[c] vs. Placebo[d]	870	817	1,691.6	286	273	98.8	17.12 (14.67, 19.98)	<0.001	Superiority is met
Overall conclusion: The superiority criteria were met.										

In children 1 to 17 years of age, the Month 12 GP-ELISA GMT for participants vaccinated with 1 dose of V920 was superior to the placebo GMT (p<0.001). Superiority was met under protocol version 4.0 (Table 13) and when data combined from both Protocol version 3.0 and 4.0 (Table 14) were analysed.

Table 13: Statistical analysis (Superiority) of V920 (1 Dose) vs. placebo in children based on Month 12 GP-ELISA GMT (GP-ELISA Per-Protocol Immunogenicity Population - Protocol version 4.0)

		Comparison Group A			Comparison Group B			Estimated Fold Difference Group A / Group B	p-value[b]	Type Specific Conclusion
Assay	Comparison Group A vs. Comparison Group B	N	n	Estimated GMT[a] (EU/mL)	N	n	Estimated GMT[a] (EU/mL)	(95% CI)		
GP-ELISA	V920 1 Dose vs. Placebo[c]	370	284	1,444.4	192	148	101.0	14.30 (11.88, 17.20)	<0.001	Superiority is met
Overall conclusion: The superiority criteria were met.										

Table 14: Statistical analysis (Superiority) of V920 (1 Dose) vs. placebo in children based on Month 12 GP-ELISA Geometric Mean Titers (GP-ELISA Per-Protocol Immunogenicity Population)

Assay	Comparison Group A vs. Comparison Group B	Comparison Group A			Comparison Group B			Estimated Fold Difference Group A / Group B	p-value[b]	Type Specific Conclusion
		N	n	Estimated GMT[a] (EU/mL)	N	n	Estimated GMT[a] (EU/mL)	(95% CI)		
GP-ELISA	V920 1 Dose vs. Placebo[c]	582	477	1,524.1	287	238	102.1	14.93 (12.90, 17.27)	<0.001	Superiority is met
Overall conclusion: The superiority criteria were met.										

Subgroup analyses in children 1 to 17 years of age (analyses by child age group, sex, and baseline serostatus) for the primary superiority analyses showed that the lower bound of the 2-sided 95% CI of the estimated GP-ELISA GMT ratio (V920 group/placebo) was greater than 1 for the antibody response for all subgroups at Day 28 for the pooled V920 group/placebo and at Month 12 for the 1-dose V920 group/placebo.

Primary and secondary immunogenicity endpoint for non-inferiority analyses

In children 1 to 17 years of age, the Day 28 GP-ELISA GMT for participants randomised to 1 or 2 doses of V920 (pooled V920) was non-inferior to the GP-ELISA GMT of adults participants randomised to 1 or 2 doses of V920 (pooled V920) with a non-inferiority margin of 0.5 ($p<0.001$) and with a non-inferiority margin of 0.67 ($p<0.001$).

The GMT ratio for children/adults was 1.42 (95% CI: 1.24, 1.62) under protocol version 4.0 (Table 15) and the GMT ratio for children/adults was 1.34 (95% CI: 1.20, 1.50) (Table 16) when data combined from both Protocol Version 3.0 and 4.0 were analysed.

Table 15: Statistical analysis (Non-inferiority, Margin=0.5) of pooled V920 in children vs. adults based on Day 28 GP-ELISA GMT (GP-ELISA Per-Protocol immunogenicity population - Protocol version 4.0)

Assay	Comparison Group A vs. Comparison Group B	Comparison Group A			Comparison Group B			Estimated Fold Difference Group A / Group B	p-value[b]	Type Specific Conclusion
		N	n	Estimated GMT[a] (EU/mL)	N	n	Estimated GMT[a] (EU/mL)	(95% CI)		
GP-ELISA	Children vs. Adults	546	499	1,748.8	558	519	1,234.4	1.42 (1.24, 1.62)	<0.001	Non-inferiority is met
Overall conclusion: The non-inferiority criteria were met.										

Table 16: Statistical analysis (Non-inferiority, Margin=0.5) of pooled V920 in children vs. adults based on Day 28 GP-ELISA GMT (GP-ELISA Per-Protocol immunogenicity population)

Assay	Comparison Group A vs. Comparison Group B	Comparison Group A			Comparison Group B			Estimated Fold Difference Group A / Group B	p-value[b]	Type Specific Conclusion
		N	n	Estimated GMT[a] (EU/mL)	N	n	Estimated GMT[a] (EU/mL)	(95% CI)		
GP-ELISA	Children vs. Adults	870	817	1,691.6	825	773	1,258.8	1.34 (1.20, 1.50)	<0.001	Non-inferiority is met
Overall conclusion: The non-inferiority criteria were met.										

In children 3 to 17 years of age, the Day 28 GP-ELISA GMT for participants randomised to 1 or 2 doses of V920 (pooled V920) was non-inferior to the GP-ELISA GMT of adults participants randomised to 1 or 2 doses of V920 (pooled V920) with a non-inferiority margin of 0.67 ($p<0.001$).

The GMT ratio for children (3-17 years)/adults was 1.50 (95% CI: 1.30, 1.72) under protocol version 4.0 and the GMT ratio for (3-17 years)/adults was 1.38 (95% CI: 1.23, 1.55) when data combined from both protocol versions 3.0 and 4.0 were analysed.

Subgroup analyses (analyses by sex and baseline serostatus) for the primary non-inferiority analysis showed that, in children (1-17 or 3-17 years of age) vs adults, the lower bound of the 2-sided 95% CI of the estimated GP-ELISA GMT ratio (pooled V920 [children/adults]) was greater than 1.0 (with a

prespecified non-inferiority margin of 0.67) for the antibody response at Day 28 for all subgroups. Data were presented for protocol version 4.0 and for combined protocol version 3.0 and 4.0.

Descriptive antibody responses data

GMT GP-ELISA

Vaccination with V920 elicited an increase in humoral immune response as observed at Day 28 through Month 12 post-vaccination, as measured by GP-ELISA, when compared to baseline.

For the overall GP-ELISA PP Immunogenicity population (children and adults combined), GP-ELISA GMTs increased after the first vaccination in the separate (1- and 2-dose V920) and pooled V920 groups, but not in the placebo group (Table 17). The GP-ELISA GMTs were higher than baseline at Day 28 for the pooled V920 group and at Month 3 and Month 12 for the 1-dose V920 group.

The GMT for the 2-dose V920 group further increased after the second vaccination (Day 56), with a 3-4 fold higher GMT measured at Month 3 as compared to Day 28 in the 2 dose V920 group. In this group, GMT decreased at Month 12 to a level comparable with the Day 28 2-dose V920 group GMT and the Month 12 1-dose V920 group GMT.

Table 17: Summary of Geometric Mean Titers (GP-ELISA Per-Protocol Immunogenicity Population - Protocol version 4.0)

Assay Time Point	V920 1 Dose (N=772) GMT (n) [95% CI]	V920 2 Dose (N=389) GMT (n) [95% CI]	Pooled V920[a] (N=1,161) GMT (n) [95% CI]	Placebo[b] (N=390) GMT (n) [95% CI]
GP-ELISA				
Day 1 (Baseline)	119.4 (730) [111.7, 127.5]	115.4 (369) [105.2, 126.7]	118.0 (1,099) [111.8, 124.6]	120.8 (367) [110.0, 132.6]
Day 28	1,501.5 (679) [1,385.2, 1,627.6]	1,392.3 (339) [1,242.1, 1,560.6]	1,464.2 (1,018) [1,370.9, 1,563.9]	115.8 (345) [103.4, 129.7]
Month 3	1,171.5 (733) [1,095.2, 1,253.0]	5,241.5 (372) [4,769.0, 5,760.8]	1,940.0 (1,105) [1,816.7, 2,071.7]	110.2 (367) [100.2, 121.2]
Month 12	1,251.4 (576) [1,159.9, 1,350.0]	1,393.5 (283) [1,250.5, 1,552.8]	1,296.5 (859) [1,218.4, 1,379.7]	110.6 (271) [99.0, 123.6]

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.
[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=1.0-mL placebo 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 contributing to the analysis.
CI=confidence interval; GMT=geometric mean titer; GP-ELISA=glycoprotein enzyme-linked immunosorbent assay.

For children aged 1-17 years (Table 18) and adults (Table 19), GP-ELISA GMTs were higher than baseline at Day 28 for the pooled V920 group and at Month 3 and Month 12 for the 1-dose V920 group. GP-ELISA GMTs were higher for children (1 to 17 years of age) compared with adults.

Table 18: Summary of Geometric Mean Titers (GP-ELISA Per-Protocol Immunogenicity Population - Protocol Version 4) (Children)

Assay Time Point	V920 1 Dose (N=386) GMT (n) [95% CI]	V920 2 Dose (N=195) GMT (n) [95% CI]	Pooled V920[a] (N=581) GMT (n) [95% CI]	Placebo[b] (N=203) GMT (n) [95% CI]
GP-ELISA				
Day 1 (Baseline)	100.3 (351) [90.6, 111.1]	98.1 (178) [85.0, 113.2]	99.6 (529) [91.6, 108.2]	103.8 (183) [90.2, 119.6]
Day 28	1,823.6 (336) [1,618.5, 2,054.7]	1,604.0 (163) [1,351.5, 1,903.8]	1,748.8 (499) [1,585.6, 1,928.7]	96.4 (173) [81.6, 113.8]
Month 3	1,282.1 (370) [1,168.6, 1,406.6]	6,602.2 (187) [5,795.4, 7,521.4]	2,222.7 (557) [2,023.7, 2,441.3]	91.2 (189) [80.1, 103.9]
Month 12	1,444.4 (284) [1,295.1, 1,610.9]	1,894.6 (139) [1,621.0, 2,214.4]	1,579.1 (423) [1,443.2, 1,727.7]	101.0 (148) [86.9, 117.5]

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.
[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=1.0-mL placebo 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 contributing to the analysis.
CI=confidence interval; GMT=geometric mean titer; GP-ELISA=glycoprotein enzyme-linked immunosorbent assay.

Table 19: Summary of Geometric Mean Titers (GP-ELISA Per-Protocol Immunogenicity Population - Protocol Version 4) (Adults)

Assay Time Point	V920 1 Dose (N=386) GMT (n) [95% CI]	V920 2 Dose (N=194) GMT (n) [95% CI]	Pooled V920[a] (N=580) GMT (n) [95% CI]	Placebo[b] (N=187) GMT (n) [95% CI]
GP-ELISA				
Day 1 (Baseline)	140.2 (379) [129.0, 152.4]	134.3 (191) [119.5, 151.0]	138.2 (570) [129.2, 147.9]	140.3 (184) [124.6, 158.1]
Day 28	1,241.2 (343) [1,116.4, 1,380.0]	1,221.2 (176) [1,053.2, 1,415.9]	1,234.4 (519) [1,132.5, 1,345.4]	139.3 (172) [119.9, 161.8]
Month 3	1,068.5 (363) [971.7, 1,175.1]	4,150.8 (185) [3,633.5, 4,741.9]	1,689.5 (548) [1,543.5, 1,849.2]	134.6 (178) [117.5, 154.2]
Month 12	1,088.4 (292) [983.5, 1,204.6]	1,035.9 (144) [896.6, 1,196.9]	1,070.8 (436) [985.6, 1,163.4]	123.4 (123) [105.5, 144.3]

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.

[a] Pooled V920=V920 1 dose or 2 dose.

[b] Placebo=1.0-mL placebo 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 contributing to the analysis.

CI=confidence interval; GMT=geometric mean titer; GP-ELISA=glycoprotein enzyme-linked immunosorbent assay.

GP-ELISA GMTs of children was generally comparable for each age subgroup of children in the V920 groups at the postvaccination timepoints (Table 20).

Table 20: Summary of Geometric Mean Titers for Children (GP-ELISA Per-Protocol Immunogenicity Population - Protocol Version 4.0)

Study Intervention Group	Day 1 (Baseline) GMT (n) [95% CI]	Day 28 GMT (n) [95% CI]	Month 3 GMT (n) [95% CI]	Month 12 GMT (n) [95% CI]
Children 1 to 17 Years				
V920 1 Dose (N=386)	100.3 (351) [90.6, 111.1]	1,823.6 (336) [1,618.5, 2,054.7]	1,282.1 (370) [1,168.6, 1,406.6]	1,444.4 (284) [1,295.1, 1,610.9]
V920 2 Dose (N=195)	98.1 (178) [85.0, 113.2]	1,604.0 (163) [1,351.5, 1,903.8]	6,602.2 (187) [5,795.4, 7,521.4]	1,894.6 (139) [1,621.0, 2,214.4]
V920 Pooled[a] (N=581)	99.6 (529) [91.6, 108.2]	1,748.8 (499) [1,585.6, 1,928.7]	NA	NA
Placebo[b] (N=203)	103.8 (183) [90.2, 119.6]	96.4 (173) [81.6, 113.8]	91.2 (189) [80.1, 103.9]	101.0 (148) [86.9, 117.5]
Children 1 to <3 Years				
V920 1 Dose (N=52)	50.2 (43) [40.2, 62.7]	1,192.1 (45) [827.6, 1,717.1]	1,092.3 (48) [847.9, 1,407.2]	1,719.3 (45) [1,245.7, 2,373.1]
V920 2 Dose (N=34)	45.4 (30) [34.8, 59.2]	1,440.2 (29) [914.1, 2,269.0]	9,117.6 (30) [6,618.1, 12,561.1]	1,853.8 (29) [1,240.9, 2,769.6]
V920 Pooled[a] (N=86)	48.2 (73) [40.7, 57.1]	1,283.8 (74) [966.7, 1,704.9]	NA	NA
Placebo[b] (N=29)	42.4 (25) [31.7, 56.7]	50.9 (28) [32.1, 80.9]	42.8 (29) [30.9, 59.2]	77.2 (24) [49.7, 120.1]

Study Intervention Group	Day 1 (Baseline) GMT (n) [95% CI]	Day 28 GMT (n) [95% CI]	Month 3 GMT (n) [95% CI]	Month 12 GMT (n) [95% CI]
Children 3 to <12 Years				
V920 1 Dose (N=203)	93.3 (180) [80.6, 108.1]	1,845.1 (171) [1,552.1, 2,193.4]	1,286.5 (197) [1,127.6, 1,467.9]	1,368.4 (153) [1,189.3, 1,574.5]
V920 2 Dose (N=96)	107.9 (83) [86.9, 133.9]	1,583.1 (76) [1,221.5, 2,051.9]	6,579.9 (92) [5,424.9, 7,980.8]	1,930.3 (67) [1,561.6, 2,386.1]
V920 Pooled [a] (N=299)	97.7 (263) [86.5, 110.3]	1,760.2 (247) [1,524.4, 2,032.5]	NA	NA
Placebo [b] (N=114)	108.4 (99) [89.0, 132.2]	97.7 (94) [77.4, 123.4]	95.1 (106) [79.4, 113.8]	100.0 (85) [82.8, 120.7]
Children 12 to 17 Years				
V920 1 Dose (N=131)	140.0 (128) [120.9, 162.2]	2,103.3 (120) [1,772.2, 2,496.4]	1,356.1 (125) [1,177.5, 1,561.7]	1,451.6 (86) [1,188.6, 1,772.8]
V920 2 Dose (N=65)	124.1 (65) [100.9, 152.5]	1,722.2 (58) [1,346.0, 2,203.4]	5,715.7 (65) [4,699.4, 6,951.8]	1,867.5 (43) [1,407.6, 2,477.6]
V920 Pooled [a] (N=196)	134.4 (193) [119.3, 151.6]	1,970.7 (178) [1,711.7, 2,268.8]	NA	NA
Placebo [b] (N=60)	141.2 (59) [113.7, 175.4]	133.3 (51) [102.5, 173.4]	126.4 (54) [102.0, 156.7]	121.9 (39) [90.6, 164.1]

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.

[a] Pooled V920=V920 1 dose or 2 dose.

[b] Placebo=1.0-mL placebo 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 contributing to the analysis.

NA=not applicable; Results for the V920 pooled group are not applicable for the Month 3 and Month 12 time points as the V920 2 Dose group received a second vaccination with V920 at Month 3.

CI=confidence interval; GMT=geometric mean titer; GP-ELISA=glycoprotein enzyme-linked immunosorbent assay.

Reverse cumulative distribution curves of GP-ELISA Titers for the 1-dose V920 groups of protocol versions 3.0 and 4.0 are over-lapping both at Day 28 (Figure 3) and Month 12 (Figure 4).

Figure 3: Reverse Cumulative Distribution Plot of Day 28 GP-ELISA Titers by Vaccination Group (GP-ELISA Per-Protocol Immunogenicity Population) (Pooled V920 and Placebo and Protocol Version 3.0 and Protocol Version 4.0)

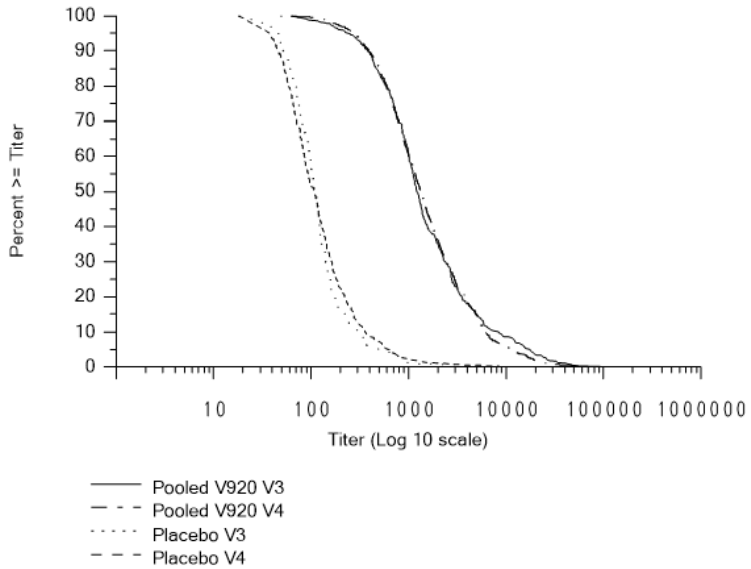
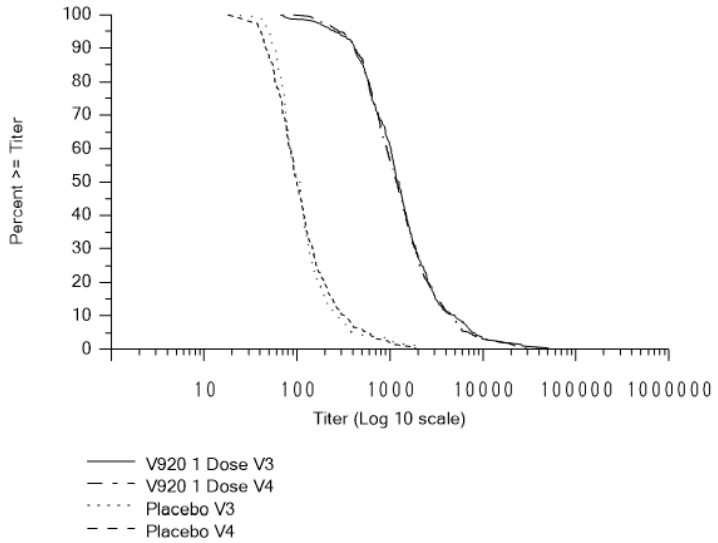


Figure 4: Reverse Cumulative Distribution Plot of Month 12 GP-ELISA Titers by Vaccination Group (GP-ELISA Per-Protocol Immunogenicity Population) (V920 1 Dose and Placebo and Protocol Version 3.0 and Protocol Version 4.0)



GMT PRNT

Vaccination with V920 elicited a humoral functional immune response through Month 12 post-vaccination as measured by the PRNT assay.

For the overall PRNT PP Immunogenicity population (children and adults combined), PRNT GMTs increased after the first vaccination in the separate (1- and 2-dose V920) and pooled V920 groups, but not in the placebo group (Table 21). The PRNT GMTs were higher than baseline at Day 28 for the pooled V920 group and at Month 3 and Month 12 for the 1-dose V920 group.

The GMT for the 2-dose V920 group further increased after the second vaccination (Day 56), with a 3-4 fold higher GMT measured at Month 3 as compared to Day 28 in the 2 dose V920 group. In this group, PRNT GMT decreased at Month 12 to levels comparable with the Day 28 2-dose V920 group GMT and the Month 12 1-dose V920 group GMT.

Table 1: Summary of GMT (PRNT Per-Protocol Immunogenicity Population - Protocol Version 4.0)

Assay Time Point	V920 1 Dose (N=412) GMT (n) [95% CI]	V920 2 Dose (N=206) GMT (n) [95% CI]	Pooled V920[a] (N=618) GMT (n) [95% CI]	Placebo[b] (N=203) GMT (n) [95% CI]
PRNT				
Day 1 (Baseline)	17.6 (376) [17.2, 18.0]	18.3 (185) [17.7, 18.9]	17.8 (561) [17.5, 18.2]	17.5 (188) [16.9, 18.1]
Day 28	246.0 (364) [225.7, 268.2]	239.2 (175) [211.2, 270.9]	243.8 (539) [227.1, 261.7]	17.8 (160) [15.6, 20.2]
Month 3	146.8 (391) [137.1, 157.3]	815.0 (194) [739.2, 898.6]	259.2 (585) [239.2, 280.9]	17.9 (182) [16.2, 19.8]
Month 12	246.5 (289) [224.6, 270.6]	298.1 (134) [259.9, 341.8]	261.8 (423) [242.3, 282.9]	17.8 (133) [15.5, 20.4]

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.
[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=1.0-mL placebo 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 contributing to the analysis.
CI=confidence interval; GMT=geometric mean titer; PRNT=plaque reduction neutralization test.

For children aged 1-17 years (Table 22) and adults (Table 23) PRNT GMTs were higher than baseline at Day 28 for the pooled V920 group and at Month 3 and Month 12 for the 1-dose V920 group. PRNT GMTs were higher for children (1 to 17 years of age) compared with adults.

Table 2: Summary of GMT (PRNT Per-Protocol Immunogenicity Population - Protocol Version 4.0) (Children)

Assay Time Point	V920 1 Dose (N=310) GMT (n) [95% CI]	V920 2 Dose (N=158) GMT (n) [95% CI]	Pooled V920[a] (N=468) GMT (n) [95% CI]	Placebo[b] (N=163) GMT (n) [95% CI]
PRNT				
Day 1 (Baseline)	17.7 (284) [17.2, 18.1]	18.1 (145) [17.5, 18.7]	17.8 (429) [17.4, 18.2]	17.5 (149) [16.9, 18.1]
Day 28	281.9 (266) [255.5, 311.0]	267.7 (133) [233.0, 307.6]	277.1 (399) [255.8, 300.2]	17.8 (130) [15.5, 20.5]
Month 3	161.1 (293) [149.4, 173.8]	919.1 (151) [827.2, 1,021.3]	291.3 (444) [266.0, 319.0]	18.0 (144) [16.1, 20.0]
Month 12	307.0 (205) [278.0, 339.1]	384.2 (103) [333.9, 442.0]	330.9 (308) [305.0, 359.0]	17.8 (109) [15.6, 20.4]

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.
[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=1.0-mL placebo 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 contributing to the analysis.
CI=confidence interval; GMT=geometric mean titer; PRNT=plaque reduction neutralization test.

Table 23: Summary of GMT (PRNT Per-Protocol Immunogenicity Population - Protocol Version 4.0) (Adults)

Assay Time Point	V920 1 Dose (N=102) GMT (n) [95% CI]	V920 2 Dose (N=48) GMT (n) [95% CI]	Pooled V920[a] (N=150) GMT (n) [95% CI]	Placebo[b] (N=40) GMT (n) [95% CI]
PRNT				
Day 1 (Baseline)	17.5 (92) [16.7, 18.4]	19.0 (40) [17.6, 20.5]	18.0 (132) [17.2, 18.7]	17.5 (39) [16.2, 18.9]
Day 28	170.1 (98) [144.1, 200.7]	167.4 (42) [129.9, 215.6]	169.2 (140) [147.4, 194.3]	17.5 (30) [13.0, 23.6]
Month 3	111.3 (98) [96.3, 128.6]	534.4 (43) [429.6, 664.7]	179.5 (141) [152.8, 210.9]	17.5 (38) [13.9, 22.1]
Month 12	144.3 (84) [122.2, 170.4]	128.3 (31) [97.6, 168.7]	139.8 (115) [121.3, 161.1]	17.5 (24) [12.8, 23.9]

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.
[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=1.0-mL placebo 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 contributing to the analysis.
CI=confidence interval; GMT=geometric mean titer; PRNT=plaque reduction neutralization test.

PRNT GMTs of children were higher for children younger than 3 years of age compared with children 3 to 11 years and 12 to 17 years of age in the 1 dose V920 group at Month 12 post-vaccination and in the 2 dose V920 group at Month 3 post-primary vaccination (Table 24).

Table 24: Summary of GMT for Children (PRNT Per-Protocol immunogenicity population - Protocol version 4.0)

Study Intervention Group	Day 1 (Baseline) GMT (n) [95% CI]	Day 28 GMT (n) [95% CI]	Month 3 GMT (n) [95% CI]	Month 12 GMT (n) [95% CI]
Children 1 to 17 Years				
V920 1 Dose (N=310)	17.7 (284) [17.2, 18.1]	281.9 (266) [255.5, 311.0]	161.1 (293) [149.4, 173.8]	307.0 (205) [278.0, 339.1]
V920 2 Dose (N=158)	18.1 (145) [17.5, 18.7]	267.7 (133) [233.0, 307.6]	919.1 (151) [827.2, 1,021.3]	384.2 (103) [333.9, 442.0]
V920 Pooled [a] (N=468)	17.8 (429) [17.4, 18.2]	277.1 (399) [255.8, 300.2]	NA	NA
Placebo [b] (N=163)	17.5 (149) [16.9, 18.1]	17.8 (130) [15.5, 20.5]	18.0 (144) [16.1, 20.0]	17.8 (109) [15.6, 20.4]
Children 1 to <3 Years				
V920 1 Dose (N=40)	17.5 (39) [<0, <0]	321.0 (33) [231.1, 445.7]	265.7 (37) [224.2, 314.7]	494.7 (32) [386.5, 633.3]
V920 2 Dose (N=25)	17.5 (25) [<0, <0]	278.4 (22) [186.2, 416.3]	1,878.9 (23) [1,515.3, 2,329.7]	462.7 (22) [343.5, 623.2]
V920 Pooled [a] (N=65)	17.5 (64) [<0, <0]	303.2 (55) [235.4, 390.5]	NA	NA
Placebo [b] (N=22)	17.5 (22) [<0, <0]	17.5 (20) [11.5, 26.7]	17.5 (20) [13.9, 22.0]	17.5 (18) [12.6, 24.3]

Study Intervention Group	Day 1 (Baseline) GMT (n) [95% CI]	Day 28 GMT (n) [95% CI]	Month 3 GMT (n) [95% CI]	Month 12 GMT (n) [95% CI]
Children 3 to <12 Years				
V920 1 Dose (N=140)	17.9 (134) [16.9, 18.8]	280.4 (114) [241.3, 325.7]	159.7 (132) [142.4, 179.2]	312.7 (88) [271.0, 360.8]
V920 2 Dose (N=68)	18.7 (66) [17.4, 20.2]	278.2 (53) [223.3, 346.7]	925.0 (63) [783.4, 1,092.2]	477.1 (39) [384.8, 591.5]
V920 Pooled [a] (N=208)	18.1 (200) [17.4, 18.9]	279.7 (167) [247.2, 316.5]	NA	NA
Placebo [b] (N=82)	17.5 (79) [16.3, 18.7]	18.1 (68) [14.9, 22.0]	18.4 (76) [15.8, 21.4]	18.2 (53) [15.1, 21.9]
Children 12 to 17 Years				
V920 1 Dose (N=130)	17.5 (111) [17.4, 17.6]	273.3 (119) [237.5, 314.6]	140.1 (124) [125.9, 155.9]	251.7 (85) [215.7, 293.7]
V920 2 Dose (N=65)	17.6 (54) [17.5, 17.8]	254.7 (58) [208.2, 311.4]	709.3 (65) [611.9, 822.1]	285.0 (42) [228.8, 354.9]
V920 Pooled [a] (N=195)	17.5 (165) [17.5, 17.6]	267.1 (177) [238.1, 299.6]	NA	NA
Placebo [b] (N=59)	17.5 (48) [17.4, 17.6]	17.5 (42) [13.8, 22.2]	17.5 (48) [14.7, 20.8]	17.5 (38) [13.9, 22.0]

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.

95% CIs with a value of "[<0, <0]" are undefined because all participants had the same titer values (less than the lower limit of quantification).

[a] Pooled V920=V920 1 dose or 2 dose.

[b] Placebo=1.0-mL placebo 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 contributing to the analysis.

NA=not applicable; Results for the V920 pooled group are not applicable for the Month 3 and Month 12 time points as the V920 2 Dose group received a second vaccination with V920 at Month 3.

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

Reverse cumulative distribution curves of PRNT Titers for the 1-dose V920 groups of protocol versions 3.0 and 4.0 are non-over-lapping both at Day 28 (Figure 5) and Month 12 (Figure 6). For both time-points, the reverse cumulative distribution curves for protocol version 4.0 appear to the right respectively to the curves for protocol version 3.0.

Figure 5: Reverse Cumulative Distribution Plot of Day 28 PRNT Titers by Vaccination Group (PRNT Per-Protocol Immunogenicity Population) – (Pooled V920 and Placebo and Protocol Version 3.0 and 4.0)

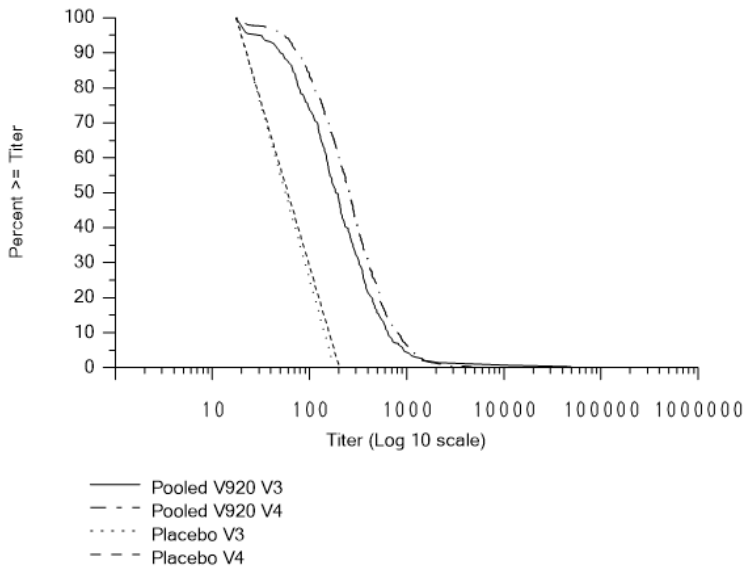
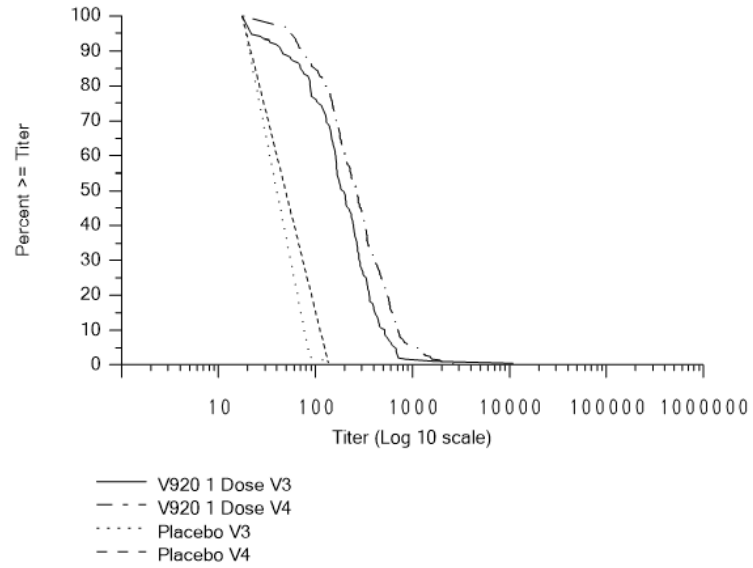


Figure 6: Reverse Cumulative Distribution Plot of Month 12 PRNT Titers by Vaccination Group (PRNT Per-Protocol Immunogenicity Population) - (V920 1 Dose and Placebo and Protocol Version 3.0 and 4.0)



Seroresponse rates

GP-ELISA seroresponse rates

Most (>94%) participants vaccinated with V920 in the overall GP-ELISA PP immunogenicity population had a seroresponse defined as ≥2-fold increase from baseline and ≥200 EU/mL at any time post-vaccination. The majority (>85%) had a seroresponse defined as ≥4-fold increase from baseline at any time postvaccination. Few (<11%) participants who received placebo had a seroresponse by either definition.

The proportions of participants with a seroresponse (≥2-fold increase from baseline and ≥200 EU/mL or ≥4-fold increase from baseline) were generally comparable for all V920 groups at Day 28. Following

second vaccination in the 2-dose V920 group, the proportion of participants with a seroresponse by either definition increased at Month 3. At Month 12, the proportion of participants in the 2-dose V920 group with a seroresponse by either definition was comparable with the proportion at Day 28 and with the 1-dose V920 group at Month 12.

Table 25: Summary of seroresponse rates (4-Fold Increase from Baseline) (GP-ELISA Per-Protocol Immunogenicity Population - Protocol Version 4.0)

Assay Time Point	V920 1 Dose (N=772) Percent (m/n) [95% CI]	V920 2 Dose (N=389) Percent (m/n) [95% CI]	Pooled V920[a] (N=1,161) Percent (m/n) [95% CI]	Placebo[b] (N=390) Percent (m/n) [95% CI]
GP-ELISA				
At any time	85.4 (614/719) [82.6%, 87.9%]	98.1 (352/359) [96.0%, 99.2%]	89.6 (966/1,078) [87.6%, 91.4%]	4.2 (15/358) [2.4%, 6.8%]
Day 28	81.3 (529/651) [78.0%, 84.2%]	82.8 (269/325) [78.2%, 86.7%]	81.8 (798/976) [79.2%, 84.1%]	1.5 (5/330) [0.5%, 3.5%]
Month 3	79.1 (550/695) [75.9%, 82.1%]	97.7 (346/354) [95.6%, 99.0%]	85.4 (896/1,049) [83.1%, 87.5%]	0.6 (2/345) [0.1%, 2.1%]
Month 12	81.8 (441/539) [78.3%, 85.0%]	81.8 (216/264) [76.6%, 86.3%]	81.8 (657/803) [79.0%, 84.4%]	3.2 (8/252) [1.4%, 6.2%]

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.
[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=1.0-mL placebo group.
Percent=m/n and represents proportion of participants with GP-ELISA ≥4-fold increase from baseline.
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.
m=number of participants who had a seroresponse.
CI=confidence interval; GP-ELISA=glycoprotein enzyme-linked immunosorbent assay.

The proportions of participants with a GP-ELISA seroresponse by either definition in the V920 groups were lower for baseline seropositive participants (GP-ELISA ≥200 EU/mL) compared with baseline seronegative participants (GP-ELISA <200 EU/mL). The proportions of participants with a GP-ELISA seroresponse by either definition was comparable for females and males in the V920 groups.

Concerning GP-ELISA seroresponse rates in the paediatric population, most (>95%) children (1 to 17 years of age) vaccinated with V920 had a seroresponse defined as ≥2-fold increase from baseline and ≥200 EU/mL at any time postvaccination and >92% of children had a seroresponse defined as ≥4-fold increase from baseline at any time postvaccination.

Table 26: Summary of seroresponse rates (4-Fold Increase from Baseline) (GP-ELISA Per-Protocol Immunogenicity Population - Protocol Version 4.0) (Children)

Assay Time Point	V920 1 Dose (N=386) Percent (m/n) [95% CI]	V920 2 Dose (N=195) Percent (m/n) [95% CI]	Pooled V920[a] (N=581) Percent (m/n) [95% CI]	Placebo[b] (N=203) Percent (m/n) [95% CI]
GP-ELISA				
At any time	92.6 (324/350) [89.3%, 95.1%]	98.9 (172/174) [95.9%, 99.9%]	94.7 (496/524) [92.4%, 96.4%]	5.7 (10/176) [2.8%, 10.2%]
Day 28	88.5 (277/313) [84.4%, 91.8%]	88.2 (134/152) [81.9%, 92.8%]	88.4 (411/465) [85.1%, 91.2%]	1.3 (2/160) [0.2%, 4.4%]
Month 3	86.7 (293/338) [82.6%, 90.1%]	98.3 (169/172) [95.0%, 99.6%]	90.6 (462/510) [87.7%, 93.0%]	0.6 (1/170) [0.0%, 3.2%]
Month 12	90.4 (226/250) [86.1%, 93.8%]	90.2 (110/122) [83.4%, 94.8%]	90.3 (336/372) [86.9%, 93.1%]	5.4 (7/129) [2.2%, 10.9%]

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.
[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=1.0-mL placebo group.
Percent=m/n and represents proportion of participants with GP-ELISA ≥4-fold increase from baseline.
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.
m=number of participants who had a seroresponse.
CI=confidence interval; GP-ELISA=glycoprotein enzyme-linked immunosorbent assay.

The proportions of participants with a seroresponse by either definition was comparable for each age subgroup of children (1 to <3, 3 to <12 and 12 to <18 years of age) in the V920 groups.

The proportions of participants with a seroresponse defined as ≥2-fold increase from baseline and ≥200 EU/mL were comparable for children and adults in the V920 groups.

The proportions of participants with a seroresponse defined as ≥4-fold increase from baseline were generally higher for children as compared to adults in the V920 groups at all time-points after vaccination.

Table 27: Summary of Day 28 seroresponse rates (4-Fold Increase from Baseline) - (Children vs. Adults) - (GP-ELISA Per-Protocol Immunogenicity Population - Protocol Version 4.0)

Assay Time Point	V920 1 Dose Percent (m/n) [95% CI]	V920 2 Dose Percent (m/n) [95% CI]	Pooled V920[a] Percent (m/n) [95% CI]	Placebo[b] Percent (m/n) [95% CI]
Children	88.5 (277/313) [84.4%, 91.8%]	88.2 (134/152) [81.9%, 92.8%]	88.4 (411/465) [85.1%, 91.2%]	1.3 (2/160) [0.2%, 4.4%]
Adults	74.6 (252/338) [69.6%, 79.1%]	78.0 (135/173) [71.1%, 84.0%]	75.7 (387/511) [71.8%, 79.4%]	1.8 (3/170) [0.4%, 5.1%]
Children - Adults	13.9 [8.1%, 19.8%]	10.2 [1.9%, 18.2%]	12.7 [7.9%, 17.4%]	-0.5 [-4.0%, 2.9%]

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.
[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=1.0-mL placebo group.
Percent=m/n and represents proportion of participants with GP-ELISA ≥4-fold increase from baseline as well as the difference in percentages between children and adults.
n=number of participants contributing to the analysis. Participant must have serology data at baseline and timepoint.
m=number of participants who had a seroresponse.
CI=confidence interval (exact 95% CIs for Children and Adult percentages, Miettinen & Nurminen 95% CIs for the difference in percentages); GP-ELISA=glycoprotein enzyme-linked immunosorbent assay.

PRNT seroresponse rates

Most (>96%) participants vaccinated with V920 in the overall PRNT PP immunogenicity population had a seroresponse defined as ≥4-fold increase from baseline at any time postvaccination. Few (<3%) participants who received placebo had a seroresponse (Table 28).

The proportions of participants with a seroresponse were comparable for all V920 groups at Day 28. Following the second vaccination in the 2-dose V920 group, the proportion of participants with a seroresponse increased at Month 3. At Month 12, the proportion of participants in the 2-dose V920 with a seroresponse was comparable with the proportion at Day 28 and to the 1-dose V920 group at Month 12.

Table 28: Summary of seroresponse rates summary of seroresponse rates (4-Fold Increase From Baseline) (PRNT Per-Protocol Immunogenicity Population - Protocol Version 4.0)

Assay Time Point	V920 1 Dose (N=412) Percent (m/n) [95% CI]	V920 2 Dose (N=206) Percent (m/n) [95% CI]	Pooled V920[a] (N=618) Percent (m/n) [95% CI]	Placebo[b] (N=205) Percent (m/n) [95% CI]
PRNT				
At any time	96.3 (360/374) [93.8%, 97.9%]	98.9 (176/178) [96.0%, 99.9%]	97.1 (536/552) [95.3%, 98.3%]	2.2 (4/183) [0.6%, 5.5%]
Day 28	92.2 (308/334) [88.8%, 94.9%]	88.5 (139/157) [82.5%, 93.1%]	91.0 (447/491) [88.2%, 93.4%]	0.6 (1/155) [0.0%, 3.5%]
Month 3	84.6 (303/358) [80.5%, 88.2%]	99.4 (173/174) [96.8%, 100%]	89.5 (476/532) [86.5%, 92.0%]	1.2 (2/170) [0.1%, 4.2%]
Month 12	91.1 (245/269) [87.0%, 94.2%]	93.5 (115/123) [87.6%, 97.2%]	91.8 (360/392) [88.7%, 94.3%]	0.8 (1/125) [0.0%, 4.4%]

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.
[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=1.0-mL placebo group.
Percent=m/n and represents proportion of participants with PRNT ≥4-fold increase from baseline.
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.
m=number of participants who had a seroresponse.
CI=confidence interval; PRNT=plaque reduction neutralization test.

The proportions of participants with a PRNT seroresponse in the V920 groups were comparable for baseline seropositive (GP-ELISA ≥200 EU/mL) and baseline seronegative participants. The proportions of participants with a PRNT seroresponse were comparable for female and male in the V920 groups.

Concerning PRNT seroresponse rates in the paediatric population, most (>95%) children vaccinated with V920 had a PRNT seroresponse at any time postvaccination. The proportions of participants with a seroresponse were comparable for children younger than 3, 3 to 11 and 12 to 17 years of age.

The proportions of participants with a seroresponse were generally comparable for children and adults, except at the Month 3 and Month 12 timepoints in the 1-dose V920 group, when children had a higher seroresponse rate compared with adults.

Ancillary analyses

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 29: Summary of Immunogenicity for trial PREVAC/V920-016

Title: Partnership for Research on Ebola VACcination (PREVAC/V920-016) A multicentre, randomised, double-blind, placebo-controlled phase 2 clinical trial of the safety and immunogenicity of three vaccine strategies against the Ebola virus in healthy volunteers 1 year of age and above.		
Study identifier	NCT02876328	
Design	multicentre, randomised, double-blind, placebo-controlled	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	First Participant First Visit: 24-Jul-2017 Last Participant Last Visit: 24-Dec-2019 (12 months, the base study) Not applicable From the end of base study (Month 12) through Month 60 (long-term follow-up for immunogenicity and SAEs)
Hypothesis	Superiority in children (≥1 to <18 years of age) of V920 to placebo for the GP-ELISA antibody response at Day 28 (1 dose), and at Month 12 for respectively 1 or 2 doses. Rejecting the null hypothesis requires the lower bound of the two-sided 95% CI of the GP-ELISA V920 / Placebo GMT ratio to be greater than 1. Non-inferiority of V920 in children (≥1 to <18 years of age) as compared to adults for the GP-ELISA antibody response at Day 28 (1 dose). Rejecting the null hypothesis requires the lower bound of the two-sided 95% CI of the GP-ELISA V920 children / adults GMT ratio to be greater than 0.5 or 0.67.	
Treatments groups	V920 (1 dose)	V920 (1.0 mL) followed by placebo (1.0 mL) at Day 56 802 participants randomised 802 participants received first vaccination 761 participants received second vaccination 773 participants completed Month 12 visit
	V920 (2 dose)	V920 (1.0 mL) followed by V920 (1.0 mL) at Day 56 399 participants randomised 399 participants received first vaccination 385 participants received second vaccination 380 participants completed Month 12 visit

	V920 matching placebo (0.5 and 1.0 mL placebo groups combined)		Placebo (0.5 mL or 1.0 mL) followed by matching placebo at Day 56 801 participants randomised 801 participants received first vaccination 773 participants received second vaccination 766 participants completed Month 12 visit 401 participants enrolled in the V920 placebo (1.0 mL) group for the immunogenicity cohort.
Endpoints and definitions	Primary Immunogenicity Endpoints	Immunogenicity - GMT	• GP-EBOV antibody response at Day 28 after randomisation (first vaccination), as measured by GP-ELISA • GP-EBOV antibody response at Month 12 after randomisation (first vaccination), as measured by GP-ELISA
	Secondary Immunogenicity Endpoints	Immunogenicity- GMT	• GP-EBOV antibody response at Day 28, Month 3, and Month 12 after randomisation (first vaccination) as measured by GP-ELISA • Neutralising antibody response at Day 28, Month 3, and Month 12 after randomisation (first vaccination), as measured by PRNT
Database lock	01-Nov-2021		

Results and Analysis

Analysis description	**Primary Superiority Immunogenicity Analysis**			
Analysis population and time point description	**Per Protocol:** all randomised and vaccinated subjects who met the inclusion criteria, did not meet exclusion criteria, did not have major protocol deviations Day 28 and Month 12 after randomisation (first vaccination)			
Descriptive statistics and estimate variability	Treatment group	V920 (pooled 1 dose)	Placebo (1.0 mL)	Ratio, superiority (95% CI) *p-value*
	Number of participants contributing to the analysis – Day28	499	173	
	GMT (95% CI)	1748.8 [1,585.6, 1,928.7]	96.4 [81.6, 113.8]	18.15 (14.96, 22.01) *<0.001*
Notes	In children 1 to 17 years of age: • The pooled V920 GMT was superior to the placebo GMT (p<0.001) at Day 28. • The 1-dose V920 GMT was superior to the placebo GMT (p<0.001) at Month 12. • The 2-dose V920 GMT was superior to the placebo GMT (p<0.001) at Month 12.			
Analysis description	**Primary and Secondary Non-Inferiority Immunogenicity Analysis**			

Analysis population and time point description	**Per Protocol:** all randomised and vaccinated subjects who met the inclusion criteria, did not meet exclusion criteria, did not have major protocol deviations Day 28 after randomisation (first vaccination)			
Descriptive statistics and estimate variability	Treatment group	V920 (pooled 1 dose) – children 1-17 yoa	V920 (pooled 1 dose) – adults	Ratio, NI (95% CI) *p-value*
	Number of participants contributing to the analysis – Day28	499	519	
	GMT (95% CI)	1748.8 [1,585.6, 1,928.7]	1234.4 [1,132.5, 1,345.4]	1.42 (1.24, 1.62) *<0.001*
Notes	• The pooled V920 GMT (after first vaccination) in children (1 to 17 years of age) was non-inferior to the pooled V920 GMT (after first vaccination) in adults (non-inferiority, margin=0.5 and 0.67, p<0.001) at Day 28. • The pooled V920 GMT in children 3 to 17 years of age was noninferior to the pooled V920 GMT in adults (non-inferiority, margin=0.67, p<0.001) at Day 28.			
Analysis description	**Secondary Analyses: Summaries of V920 Antibody Responses in Children 1 to 17 Years of Age and Adults as Measured by GP-ELISA and PRNT**			
Analysis population and time point description	**Per Protocol:** all randomised and vaccinated subjects who met the inclusion criteria, did not meet exclusion criteria, did not have major protocol deviations Day 28 and Month 12 after randomisation (first vaccination)			
Descriptive statistics and estimate variability	Treatment group	V920 (1 dose)	V920 (2 dose)	Placebo (1.0 mL)
	Day 28 GP-ELISA GMT [95% CI] (N) N° contributing to analysis	1,501.5 [1,385.2, 1,627.6] (679)	1,392.3 [1,242.1, 1,560.6] (339)	115.8 [103.4, 129.7] (345)
	Day 28 PRNT GMT [95% CI] (N) N° contributing to analysis	246.0 [225.7, 268.2] (364)	239.2 [211.2, 270.9] (175)	17.8 [15.6, 20.2] (160)
	Day 28 PRNT GMT [95% CI] (N) N° children (1-17yoa) contributing to analysis	281.9 [255.5, 311.0] (266)	267.7 [233.0, 307.6] (133)	17.8 [15.5, 20.5] (130)
	Month 12 GP-ELISA GMT [95% CI] (N) N° contributing to analysis	1,251.4 [1,159.9, 1,350.0] (576)	1,393.5 [1,250.5, 1,552.8] (283)	110.6 [99.0, 123.6] (271)

	Month 12 PRNT GMT [95% CI] (N) N° contributing to analysis	246.5 [224.6, 270.6] (289)	298.1 [259.9, 341.8] (134)	17.8 [15.5, 20.4] (133)
Notes	• GP-ELISA and PRNT GMTs increased after vaccination in the 1- and 2 dose V920 groups, but not in the placebo group. • GP-ELISA and PRNT GMTs were higher to baseline and to placebo at M12 both in 1-dose and 2-dose V920 • GP-ELISA and PRNT GMTs were higher for children (1 to 17 years of age) compared with adults at the postvaccination timepoints			

2.4.3. Discussion on clinical immunogenicity

No efficacy studies were conducted in the new targeted population. However, as recommended by the SAGE on immunisation, V920 was administered in children over 6 months old and in pregnant and lactating women under a compassionate use clinical protocol during the 2018-2020 outbreak in the DRC. The MAH is asked to provide available effectiveness data for the paediatric population from V920-EAP5 (category 3 study of the RMP).

Hence this application is supported by safety and immunogenicity outcomes. Immune response in vaccinated children and in placebo as well as in vaccinated children and adults were compared based on comparing ELISA IgG antibody titres. Neutralising Ab was also measured in a subset of participants. In the absence of a defined ICP for EVD, it is deemed acceptable to rely on the humoral immunogenicity outcomes to reasonably assume a benefit of V920 in protecting children.

Design and conduct of PREVAC/V920-016

This study was designed as a Phase II, multicentre, randomised, double-blind, placebo-controlled study of 2 leading Ebola vaccine candidates (Ad26.ZEBOV/MVA-BN-Filo and V920) and 3 vaccine strategies (Ad26.ZEBOV/MVA-BN-Filo, 1-dose V920, and 2-dose V920 administered with a 56 days interval).

The selected populations are overall deemed as adequate. The study was conducted in four West African countries historically at risk of ZEBOV outbreaks and several other clinical trials to study vaccines against EVD have been conducted or are ongoing in these countries. Participants with previous history of EVD or vaccination against Ebola were to be excluded. The intended study population thus reflected the population who might benefit from vaccination. It is however noted that region (urban or rural) was not included as a covariate in the ANOVA model used for the immunogenicity analyses, which is considered a study limitation.

Overall, the trial design is deemed acceptable to reach the primary and secondary immunogenicity outcomes, but some limitations in the conduct of the study have been noted.

The study protocol was amended 4 times and V920 was only administered under amended protocol version 3.0 (5-May-2017) and amended protocol version 4.0 (15-Mar-2018).

Participants randomised to V920 under protocol version 4.0 were not all administered identical actual doses of V920. Two different lots were used, i.e., lot WL00063635 corresponding to a final potency of approximately 1.3E8 pfu/mL and lot WL00067929 corresponding to a final potency of approximately 3.0E8 pfu/mL. Under protocol version 3.0, 2-fold diluted V920 from an identical drug product lot irrespective from trial site (corresponding to a potency level of approximately 5E7 pfu/mL) was administered.

Dose-adjustment recommendations were issued by WHO during the DRC outbreaks (SAGE on immunisation interim recommendations on vaccination against EVD on 7-May-2019) and head-to-head

comparisons of V920 adjusted doses with full dose of V920 (to be conducted preferably in Africa) was identified as a research need by WHO. As it is considered likely that similar dose-adjustment strategies might be recommended in future EVD outbreaks, immunogenicity data generated under protocol version 3.0 were considered relevant supportive data in the context of this extension of indication application.

The overall sample size calculation is deemed appropriate. However, a major limitation of the study design is that no sample size for each paediatric age category (1 to <3, 3 to <12 and 12 to <18 years of age) was pre-specified. The age stratification for enrolment was as per protocol, i.e., 12 to 17, 5 to 11, and 1 to 4 years of age whereas the safety and immunogenicity analyses were performed on the age strata according to the SAP, following the PDCO request (i.e., 1 to <3, 3 to <12 and 12 to <18 years of age). This resulted in different number of subjects included in each of the 3 paediatric age categories and in a very limited number of children aged 1 to <3 years of age randomised (in total 155 randomised children aged 1 to <3 years of age, as compared to 515 aged 3 to <12 years and 328 aged 12 to <18 years). It is therefore difficult to draw firm conclusions on the safety and immunogenicity in this subpopulation. Moreover, number of participants aged 1 to <3 years included in the PP immunogenicity populations were even more limited with 115 included in the GP-ELISA PP immunogenicity population (among which 52 randomised to V920 [1 dose]) and 87 included in the PRNT PP immunogenicity population (among which 40 randomised to V920 ([1 dose]). In this age subgroup, relative distribution of age was however acceptable, with approximately 40% aged ≥1 to <2 years and approximately 60% aged ≥2 to <3 years in both GP-ELISA and PRNT PP immunogenicity populations. An additional study in young children is ongoing (V920-014) and final CSR is expected in 2024 **(REC)**.

The primary and secondary objectives are endorsed. The primary immunogenicity outcomes rely on the comparison of the ZEBOV GP specific humoral immune response in children as compared to placebo (superiority) and in vaccinated children as compared to vaccinated adults (non-inferiority) based on GP-ELISA IgG antibody titres. Moreover, neutralising antibody-responses were also measured in a subset of participants to address secondary immunogenicity outcomes (by using $PRNT_{60}$). Whether GP-ELISA and/or PRNT correlate with protection is not known, but in the absence of a defined ICP for EVD, it is deemed acceptable to rely on the humoral immunogenicity outcomes to reasonably assume a benefit of V920 in protecting children. The margin chosen to demonstrate the NI (lower bound of the 2-sided 95% CI greater than 0.5) of the immune response in children compared to adults as part of the primary objective is considered not very stringent as it is expected that the children mount a higher antibody response following vaccination compared to adults. However, as a more stringent margin (lower bound of the 2-sided 95% CI greater than 0.67) is used to demonstrate NI of the immune response in children comparted to adults as secondary endpoint, this is considered acceptable. NI was not planned to be calculated for age subgroup which would have been valuable.

The PP population was the primary population for the analysis of immunogenicity data. Primary immunogenicity results were based on data from protocol version 4.0. PRNT testing was conducted on more than half of children included in the PP GP-ELISA immunogenicity population. This is in accordance with the request from the PDCO to test at least 50% of the sera by virus neutralisation. Supportive immunogenicity data were also generated under version 3.0 and detailed descriptive data was not submitted.

The statistical methods are overall appropriate.

Immunogenicity had to be summarized by presenting different parameters including seroprotection if an immunological correlate of protection was found based on data of previous studies. Data of study V920-018 were previously submitted and an attempt to define an ICP (in conjunction with the results of V920-010) was done (procedure EMEA/H/C/004554/II/0007/G). There were various limitations of the approach for the analysis of the correlate of protection. Whether GP-ELISA and/or PRNT are a correlate of protection is not known.

The seroresponder definitions are arbitrary, but similar to those used at MAA, hence deemed acceptable.

Blood sampling in adults and children for immunogenicity testing and future research were planned at baseline, Day 7, Day 14, Day 28, Day 56, Day 63, Month 3, Month 6, Month 12. The following day ranges were allowed: ±6 for Day 28, ±16 for Month 3 and ±21 for Month 12 timepoints. However, a substantial number of samples were out-of-day range, and thus excluded from the PP immunogenicity population. To include more participants in the key primary and secondary immunogenicity analyses, post hoc analyses that removed restrictions for the prespecified day ranges at each immunogenicity analysis time point were conducted.

Blood samples obtained at early time-point after first vaccination (Day 7 and Day 14) were to be used to address immediacy of immune responses by comparing the antibody responses between V920 vaccinated participants and the placebo group. The MAH was requested to provide additional antibody responses data (Day 7 and Day 14 time-points but was unable to provide such data, as Day 7 and Day 14 samples were not tested with validated GP-ELISA and PRNT assays.

Some secondary objectives described in the protocol that are not addressed by the MAH are considered relevant to support this application (refer to blood samples above).

Another secondary objective described in the protocol but not addressed by the MAH relates to the comparison of T cell and memory B cell responses for the three vaccine strategies versus placebo in a subsample of adults. Such objective would have been relevant also for younger participants, which have an immature / in development immune system as compared to adults.

In the SAP and in the Protocol version 5.0, long-term follow up of antibody responses at 24, 36, 48 and 60 months following randomisation is mentioned as a secondary objective. This application is supported only by results from the base-study, which is deemed acceptable, but the results of the long-term antibody response follow-up should be provided as soon as available **(REC).**

Results

Data obtained for the base study (12-months period after randomisation) for V920 and placebo mainly related to protocol version 4.0 were submitted, and data related to version 3.0 were partially presented in the CSR and during the assessment of this application.

Under protocol version 4.0, participant characteristics of the randomised children and adults (for all randomised participants and for GP-ELISA PP immunogenicity population) were comparable across study intervention groups. In the different age subgroups males were in general overrepresented, but their percentages never exceed 60%.

Concerning protocol version 3.0, only combined (children and adults) demographic characteristics of all randomised participants were reported in the CSR and these were overall comparable across the study interventions to those of version 4.0. Only 18 children aged 1 to <3 years were recruited (8 were aged 1 to <2 and 10 were aged 2 to <3), females were overrepresented in this age subgroup.

Mean BMI in the paediatric and adult population were comparable across study interventions. Mean BMI for children was of 16.5 (SD=2.6, median=15.9) with a wide range of 9 to 33. A higher mean BMI of 23.6 (SD=4.8, median=22.3) was reported for adults, also with a wide BMI range (16 to 50).

Data on race and prior and concomitant medications/vaccinations were not collected and are therefore not reported in the CSR. Participants having received or having taken their own medication for fever and pain following vaccination were to be recorded according to the protocol. Fever was reported with a higher frequency in children <3 years of age when compared to both other age strata. It is not known if

medication against fever and pain was more often/systematically offered to children <3 years of age during the conduct of the study. The impact on immunogenicity is neither known.

Baseline serology results obtained are consistent to those observed in adults at the time of MAA (studies V920-009 and V920-011), with a higher proportion of adults seropositive at baseline (23.7%) as compared to the paediatric subjects (17.7%), which is expected and acceptable.

As in the CSR, impact of baseline serostatus is addressed in detail in subgroup analyses, this is deemed acceptable.

Primary immunogenicity endpoints for superiority analyses

Superiority was formally demonstrated at Day 28 for children randomised to 1 and 2 doses of V920 as compared to placebo (1.0 mL) and at Month 12 separately for children respectively randomised either to 1 or 2 doses of V920 as compared to placebo ($p<0.001$).

It seems that superiority as compared to placebo was met also under Protocol Version 3.0. With vaccination with 1 dose of V920 in children 1 to 17 years of age resulting in superior GP-ELISA GMT as compared to placebo (1.0 mL) both at Day 28 and Month 12 after randomization. Fold Differences were of 15.56 (95% CI: 12.04, 20.12) and of 15.87 (95% CI: 12.50, 20.15) respectively for Day 28 (pooled V920) and Month 12 (1 dose V920) after randomisation. The lower bound of the 2-sided 95% CI of the estimated GP-ELISA GMT ratio (V920 group/placebo) was greater than 1 for both Day 28 and Month 12. For Protocol Version 3.0, the MAH did not provide the p-value for the comparison of the GMT ratio to the lower bound as provided for Protocol Version 4.0 and for combined Protocol Version 3.0 and 4.0.

Post hoc analyses that removed restrictions for the prespecified day ranges at each immunogenicity analysis time point were conducted for key primary and secondary immunogenicity analyses of protocol version 4.0. Similar results as for the primary analysis were obtained. In the Post-hoc analysis, fold differences were of 17.22 (95% CI: 14.31, 20.72) for Day 28 (pooled V920) as compared to 18.15 (95% CI: 14.96, 22.01) in the primary analysis (pooled V920). For Month 12 after randomization, fold Differences were of 14.29 (95% CI: 12.21, 16.74) in the post-hoc analysis (1 dose V920) as compared to 14.30 (95% CI: 11.88, 17.20) in the primary analysis (1 dose V920).

Subgroup analyses in children 1 to 17 years of age (analyses by child age group, sex, and baseline serostatus) for the primary superiority analyses for protocol version 4.0 and for combined protocol versions 3.0 and 4.0 were presented. For protocol version 3.0, no such subgroup analyses in children 1 to 17 years of age were presented.

The presented data showed higher responses in V920 vaccinated as compared to placebo in children 1-17 years of age with a lower bound of the 2-sided 95% CI of the estimated GP-ELISA GMT ratio (V920 group/placebo) >1 for the antibody response for all subgroups at Day 28 for the pooled V920 group/placebo and at Month 12 for the 1-dose V920 group/placebo.

Fold Differences for Day 28 (pooled V920) after randomisation were of 25.20 (95% CI: 14.66, 43.31) for children younger than 3 years; of 18.02 (95% CI: 13.70, 23.70) for children aged 3 to 11 years; and of 14.78 (95% CI: 10.97, 19.93) for children aged 12 to 17 years. Fold Differences for Month 12 (1 dose V920) after randomisation were of 22.26 (95% CI: 12.73, 38.93) for children younger than 3 years; of 13.69 (95% CI: 10.82, 17.31) for children aged 3 to 11 years; and of 11.90 (95% CI: 8.44, 16.79) for children aged 12 to 17 years. 95% CI were particularly wide for children younger than 3 years.

For the children aged 1 to <3 years, less than 80 children contributed to the Day 28 subgroup analysis and less than 50 children contributed to the Month 12 subgroup analysis under protocol version 4.0. These numbers are limited.

Moreover, such low numbers might not allow robust conclusion on potential differences in immune responses to V920 stratified by sex in children aged 1 to <3 years, which is deemed important to investigate. Higher responses to some vaccines in young girls as compared to young boys were documented. The requested additional data provided support sex-dependent differences in humoral immune responses to V920, with trends towards higher responses in female (maintained up to 12 months post-vaccination with a single dose of V920) as compared to male of all age categories.

It is agreed with the MAH that sample size does not allow to draw any firm conclusions with respect to different levels of humoral responses induced by V920 in male as compared to female participants of different age categories. In the absence of ICP, the clinical relevance is unknown.

Primary and secondary immunogenicity endpoint for non-inferiority analyses

When humoral responses measured in the paediatric population were compared to those in the adult population (formal non-inferiority tested only for Day 28 after randomisation, non-inferiority margins of 0.5 and 0.67), it can be concluded that GP-ELISA GMTs are non-inferior in children as compared to adults. Obtained data are rather indicative of higher humoral (binding and neutralizing antibodies) responses in vaccinated children as compared to adults. Increased immunogenicity to vaccines is in general expected when lowering the age of vaccinees.

For Protocol Version 3.0, it seems that non-inferiority in Day 28 GP-ELISA GMT of children aged 1-17 years or 3-17 years as compared to adults were also met. With lower bound of the 2-sided 95% CI greater than 1 and identical Day 28 GMT ratios of 1.23 (95% CI: 1.00, 1.50) for children (1-17 years)/adults and for children (3-17 years)/adults. The MAH did not provide the p-value for the comparison of the GMT ratio to the lower bound (0.5 or 0.67) as provided for protocol version 4.0 and for combined protocols.

Concerning post-hoc analysis (removing restrictions for the prespecified day ranges) conducted only for protocol version 4.0, similar results were obtained. At Day 28 after vaccination, GMT ratios were of 1.43 (95% CI: 1.26, 1.63) in the post-hoc analysis as compared to 1.42 (95% CI: 1.24, 1.62) in the primary analysis for vaccinated children aged 1-17 years compared to adults.

The MAH specified that sample size did not allow to apply in subgroup non-inferiority analyses the same age stratification used in the subgroup superiority analyses (namely 1 to <3, 3 to <12 and 12 to <18 years of age).

Descriptive antibody responses data

Vaccination with V920 elicits a humoral (binding and neutralising) immune response as observed at Day 28 through Month 12 as measured by GP-ELISA and by PRNT is endorsed. This is true for the overall PP Immunogenicity population, when combining the paediatric and adult participants and when analysing separately adults and children and consistent also with respect to the submitted GP-ELISA GMFI and PRNT GMFI results and with the data of the post-hoc analyses. GP-ELISA GMTs and PRNT GMTs levels measured after vaccination appear comparable to the levels reported for adults at the time of the initial MAA.

A similar conclusion can be drawn based on the GP-ELISA GMT, GP-ELISA GMFI, PRNT GMT and PRNT GMFI results of the overall PP Immunogenicity population of protocol version 3.0, which indicate that vaccination with V920 elicits a durable immune response from Day 28 through Month 12.

When GP-ELISA results of protocol version 4.0 are compared to those of version 3.0, it seems that comparable GMTs were measured. This is further corroborated by the reverse cumulative distribution curves of GP-ELISA Titers are overlapping both at Day 28 and Month 12 for participants vaccinated with a single dose of V920 under protocol version 3.0 and 4.0. despite administration of a dose of V920 that is

below the minimum licensed potency value under protocol version 3.0 (final potency of administered dose of approximately 5E7 pfu).

When $PRNT_{60}$ results of protocol version 4.0 are compared to those of version 3.0, it seems however that higher GMTs were measured under protocol version 4.0. Under both versions, PRNT baseline immunity was comparable. The fact that neutralizing antibody responses measured by $PRNT_{60}$ following vaccination with a single dose of V920 are higher for protocol version 4.0 is further corroborated by the reverse cumulative distribution curves of PRNT Titers that are non-overlapping both at Day 28 and Month 12 for participants vaccinated with a single dose of V920. Statistical significance of the differences in the $PRNT_{60}$ results was not discussed by the MAH and clinical relevance of the differences in $PRNT_{60}$ results is unknown in the absence of a defined ICP for EVD.

Under protocol version 4.0, participants were recruited in all the 4 countries and 6 sites (35% in Guinea, 25% in Sierra Leone, 22% in Mali, and 17% in Liberia), while under protocol version 3.0 a majority of approximately 75% of participants were recruited in Guinea and the remaining in Liberia. In addition, participants randomised to V920 under protocol version 4.0 were not all administered identical actual doses of V920. The 204 participants randomised to V920 in Liberia were administered undiluted V920 Lot WL00063635 and the 996 participants randomised to V920 in Guinea Country, Mali, and Sierra Leone (respectively 428, 265 and 303) were administered undiluted V920 lot WL00067929. On the other hand, all participants randomised to V920 under protocol version 3.0 (Guinea Country and Liberia) were administered identical actual doses of V920 from an identical drug product lot.

In order to rule out a country-bias and a drug product lot bias in the measured antibody responses, the MAH was requested to provide descriptive GP-ELISA and PRNT GMT data for participants randomised in Guinea and Liberia separately for Protocol Version 3.0 and 4.0.

Overall, submitted data do not indicate major country- and drug product lot- biases in antibody measured immune responses.

The MAH stated that GP-ELISA GMTs and PRNT GMTs were higher for children (1 to 17 years of age) compared with adults. The MAH did not clarify if GP-ELISA GMTs were higher for children (1 to 17 years of age) compared with adults also under protocol version 3.0.

Overall, submitted graphs for protocol version 4.0 support the MAH's conclusion that vaccination with V920 elicits a humoral (binding and neutralising) immune response at Day 28 and Month 12 in all paediatric age-categories (as measured by GP-ELISA and by PRNT assays), with no major notable differences in the different paediatric age-categories.

However, when GP-ELISA GMT are compared in the different paediatric age subgroups (namely 1 to <3, 3 to <12, and 12 to <18 years of age) randomised to 1 dose V920 under Protocol Version 4.0, it was noted that in children aged 3 to <12 years and in children aged 12 to <18 years GMTs decrease between Day 28 and Month 3 and that GMTs are comparable between Month 3 and Month 12. However, in children aged 1 to <3 years, GP-ELISA GMTs were comparable between Day 28 and Month 3 but GMTs increased between Month 3 and Month 12, which is an unexpected trend of the antibody response following vaccination. The MAH provided graphs representing individual trajectories of GP-ELISA and PRNT responses for children aged 1 to <3 years and children aged ≥3 to <18 years, which indicated that trends in the immunogenicity responses measured by GP-ELISA and PRNT assays are comparable and consistent for both age categories.

Concerning PRNT GMT, the MAH was requested to provide an explanation for the fact that a drop in PRNT titres at Month 3 followed by an increase in PRNT titers at Month 12 was observed in all age groups. In that respect, data of the primary analysis and of the post-hoc analysis were consistent. Such kinetic of the PRNT response was consistent with clinical previously generated. The mechanisms behind this kinetic of PRNT responses following vaccination with V920 are not elucidated. The MAH hypothesises that initial

elevation in PRNT responses is driven by low affinity IgG and IgM neutralising antibodies, which wanes prior to subsequent affinity maturation. The latter would lead to an overall increase in binding affinities and neutralisation potency at the later timepoints. It is not fully clear to which previous clinical data (with the licensed dose level) the MAH refers (Month 3 PRNT data not found) but it is agreed with the MAH that the clinical relevance of the observed kinetic of PRNT responses is unknown.

When GP-ELISA and PRNT results were analysed by baseline serostatus of participants (baseline seronegative or baseline seropositive GP-ELISA ≥200 EU/mL), GP-ELISA GMTs were generally higher for baseline seropositive participants as compared to baseline seronegative participants and GP-ELISA GMFIs were impacted by baseline serostatus. Noteworthy, baseline serostatus of participants did not have a pronounced impact on PRNT GMTs or PRNT GMFIs.

The observation that baseline serostatus of participants did not have a pronounced impact on PRNT GMTs or PRNT GMFIs, along with the observation that PRNT GMTs measured under Protocol Version 3.0 were lower as compared to those measured under protocol version 4.0, while GP-ELISA GMTs are comparable between versions 3.0 and 4.0 is unexpected. Binding and nAb might have a different kinetic of response following vaccination or such difference might also be due to the limited sample size. The clinical relevance of this observation is not known.

Seroresponse rates

Overall, the GP-ELISA seroresponse rates by either definition (≥2-fold increase from baseline and ≥200 EU/mL or ≥4-fold increase from baseline) measured in adults of the PREVAC/V920-016 study was comparable to the seroresponse rates that were reported at the time of MAA. A trend for slightly higher PRNT seroresponse rates measured at Day 28 and Month 12 in adults of the PREVAC/V920-016 were observed when compared to the seroresponse rates that were reported at the time of MAA (V920-009). 95% CI overlapped.

When GP-ELISA seroresponse rates measured under protocol version 4.0 are compared to those of version 3.0, it seems that very comparable seroresponse rates by either definition was achieved.

Under protocol version 4.0, the proportions of participants with a GP-ELISA seroresponse defined as ≥4-fold increase from baseline were generally higher for children as compared to adults in the V920 groups at all time-points after vaccination. This was also observed under protocol version 3.0.

A drop at Month 3 followed by an increase at Month 12 was also observed for PRNT seroresponse rates in all age groups. Higher rates were observed under protocol version 4.0 as compared to version 3.0. This is also consistent with descriptive PRNT antibody responses data discussed previously.

Concerning the impact of baseline immunity on GP-ELISA seroresponse rates and PRNT seroresponse rates, as expected the proportions of participants with a GP-ELISA seroresponse by either definition in the V920 groups were lower for baseline seropositive participants (GP-ELISA ≥200 EU/mL) compared with baseline seronegative participants (GP-ELISA <200 EU/mL). Nevertheless, the proportions of PRNT responders were comparable for baseline seronegative and baseline seropositive (GP-ELISA ≥200 EU/mL) participants. This is also consistent with descriptive GP-ELISA and PRNT antibody responses data described previously.

Comparable data were obtained in the primary and post-hoc analyses (removing restrictions for the prespecified day ranges) for GP-ELISA seroresponse rates by definition and PRNT seroresponse rates. No comparison of GP-ELISA seroconversion and PRNT seroconversion rates of protocol versions 3.0 and 4.0 was provided.

Booster dose

Humoral immunogenicity data was generated in subjects randomised to 2 doses of V920 (administered with an interval of 56 days). Increased GP-ELISA GMTs and GMFIs, and increased PRNT GMTs and GMFIs were measured at Month 3 as compared to participants vaccinated with a single dose of V920. However, humoral responses measured at Month 12 indicate that comparable responses were induced in participants randomised to 1 dose of V920 as compared to 2 doses of V920 at this later time-point. Therefore, the MAH concluded that though the second dose of V920 was immunogenic, no advantage of the booster dose (administered with an interval of 56 days) was observed at 12 months as compared to a single dose of V920. This conclusion is endorsed. The MAH mentioned that a clinical study determining the effect of a booster V920 dose given at a wider interval (18 months) is ongoing (PREPARE - V920-013) but no data were submitted in this application (already requested as a REC before this application).

2.4.4. Conclusions on the clinical immunogenicity

The reported humoral immunogenicity data collectively indicate that immunisation with 1 dose of V920 induces an increase in both neutralising and binding antibody titers against the vaccine virus and ZEBOV-GP, respectively, when compared to baseline, both in children 1 to 17 years of age and adults. Responses in children are non-inferior to those measured in adults and humoral responses higher than baseline values are maintained up to 1-year post-vaccination.

Limited number of children aged 1 to <3 years of age were randomised in V920-016 study, with for example less than 50 children contributing to GP-ELISA subgroup analysis. These numbers are considered limited to draw firm conclusions on the immunogenicity in this subpopulation and additional immunogenicity data from ongoing studies should be submitted when available. However, immune responses were detected in the majority of children less than 3 years following vaccination, with no major concern and seroresponse rates were higher than 80% at Day 28.

Recommendations (REC) are considered necessary to address issues related to immunogenicity (see section 3.8 – Conclusions).

2.5. Clinical safety

Introduction

Brief summary of the existing safety profile of Ervebo in the existing indication:

Anaphylaxis was reported very rarely (0.006%) in clinical trials. The most common injection-site adverse reactions were injection-site pain (70.3%), swelling (16.7%) and erythema (13.7%). The most common systemic adverse reactions reported following vaccination were headache (36.9%), pyrexia (34.3%), myalgia (32.5%), fatigue (18.5%), arthralgia (17.1%), nausea (8.0%), chills (6.3%), arthritis (3.7%), rash (3.6%), hyperhidrosis (3.2%), and abdominal pain (1.4%).
In general, these reactions were reported within 7 days after vaccination, were mild to moderate in intensity, and had short duration (less than 1 week).

Key safety endpoints:

- Solicited injection-site AEs and solicited systemic AEs of any grade severity, and Grade 3 or 4 unsolicited AEs after first vaccination and through Days 7, 14, and 28 after first vaccination

- Solicited injection-site AEs and solicited systemic AEs of any grade severity, and Grade 3 or 4 unsolicited AEs after second vaccination, through Day 7 after second vaccination, and through Month 1 after second vaccination

- SAEs through Month 12.

Exposure

In the study V920-016, a total of 2002 participants (998 children, 1004 adults) were randomised to the V920 and placebo groups under Protocol Version 4.0 (approved dose). All participants received the first vaccination and most (95.9%) received both vaccinations to which they were randomised.

The APaT population consisted of 2000 randomised participants (996 children, 1004 adults) who received at least 1 dose of V920, 0.5-mL placebo, or 1.0-mL placebo.

Two participants (1 child in the 1-dose V920 group and 1 child in the placebo group) received an incorrect study intervention and were excluded from the APaT population.

Demographic and other characteristics of study population

Demographic characteristics were generally comparable across study intervention groups for children. The median age for children was 8.0 years (range: 1 to 17 years); 15.5% of children randomised were 1 to <3 years of age, 51.6% were 3 to <12 years of age, and 32.9% were 12 to 17 years of age. Approximately half (54.7%) were male, and none were HIV-positive.

Table 30 Participants Characteristics

	V920 1 Dose		V920 2 Dose		Pooled V920[a]		Placebo[b]		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	407		202		609		389		998	
Sex										
Male	222	(54.5)	117	(57.9)	339	(55.7)	207	(53.2)	546	(54.7)
Female	185	(45.5)	85	(42.1)	270	(44.3)	182	(46.8)	452	(45.3)
Age (Years)										
<3	56	(13.8)	39	(19.3)	95	(15.6)	60	(15.4)	155	(15.5)
3 to 11	213	(52.3)	97	(48.0)	310	(50.9)	205	(52.7)	515	(51.6)
12 to 17	138	(33.9)	66	(32.7)	204	(33.5)	124	(31.9)	328	(32.9)
≥18	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Mean	8.6		8.2		8.4		8.3		8.4	
SD	4.9		5.1		5.0		5.0		5.0	
Median	9.0		8.0		9.0		8.0		8.0	
Range	1 to 17		1 to 17		1 to 17		1 to 17		1 to 17	
Race										
Missing	407	(100.0)	202	(100.0)	609	(100.0)	389	(100.0)	998	(100.0)
HIV Status										
Negative	407	(100.0)	202	(100.0)	609	(100.0)	389	(100.0)	998	(100.0)
Height (cm) at Day 1										
Participants with data	407		202		609		389		998	
Mean	127.5		125.0		126.7		125.7		126.3	
SD	28.5		29.2		28.7		28.8		28.8	
Median	132.0		127.5		130.1		126.0		129.0	

	V920 1 Dose		V920 2 Dose		Pooled V920[a]		Placebo[b]		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Range	66 to 179		70 to 185		66 to 185		64 to 186		64 to 186	
Weight (kg) at Day 1										
Participants with data	407		202		609		389		998	
Mean	29.3		27.9		28.8		28.3		28.6	
SD	15.8		15.5		15.7		15.7		15.7	
Median	25.5		23.8		25.0		24.4		24.9	
Range	7 to 72		7 to 87		7 to 87		8 to 78		7 to 87	
BMI										
Participants with data	407		202		609		389		998	
Mean	16.6		16.4		16.5		16.4		16.5	
SD	2.6		2.5		2.5		2.8		2.6	
Median	15.8		15.9		15.8		15.9		15.9	
Range	9 to 28		13 to 30		9 to 30		10 to 33		9 to 33	

[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=0.5- and 1.0-mL placebo groups.
BMI=body mass index; SD=standard deviation.

With Protocol Version 4, the number of children by age categories are:

- From 12 to 17 years of age: 204 who received 1 dose of V920 (138 children in the 1 dose group and 66 children in the 2-dose group)

- From 3 to 11 years of age: 310 who received 1 dose of V920 (213 children in the 1 dose group and 97 children in the 2-dose group)

- From 1 to 3 years of age: 95 who received 1 dose of V920 (56 children in the 1 dose group and 39 children in the 2-dose group):

    - From 2 to 3 years of age: 54 children were vaccinated with V920

    - From 1 to <2 years of age: 41 children were vaccinated with V920

With Protocol Version 3, the number of children by age categories are approximatively:

- From 12 to 17 years of age: 181 who received 1 dose of V920 (127 children in the 1 dose group and 54 children in the 2-dose group)

- From 3 to 11 years of age: 152 who received 1 dose of V920 (103 children in the 1 dose group and 49 children in the 2-dose group)

- From 1 to 3 years of age: 10 who received 1 dose of V920 (8 children in the 1 dose group and 2 children in the 2-dose group)

Demographic characteristics were generally comparable across study intervention groups for adults. The median age for adults was 27.0 years (range: 18 to 76 years); 98.2% of adults were between the ages of 18 and 65 years. Approximately half (54.6%) were male, and 1.9% were HIV-positive.

Adverse events

The pooled V920 group was used to describe the safety of V920 compared with placebo in the safety follow-up period after the first vaccination and the 2 dose V920 group was used to describe the safety of V920 in the safety follow-up period after the second vaccination. Results were considered comparable if the percent difference between groups was <10% and higher or lower if the percent difference was >10%.

The analyses of AEs for participants randomised under protocol version 3.0 (diluted V920) and protocol version 4.0 indicate that V920 was generally well tolerated in children and adults who received a 1-dose or 2-dose regimen. No vaccine-related SAEs were reported for any participants.

With protocol version 4.0, the majority of children and adults experienced 1 or more AEs from the first vaccination visit to Day 28 after first vaccination. The proportions of children (85%) and adults (76%) who experienced an injection-site AE or non injection-site AE were higher in the pooled V920 group compared with the placebo group (+/- 66%), with the greatest difference observed for injection-site AEs. Fewer than half of children and adults in the pooled V920 and placebo groups experienced 1 or more injection-site AE; the majority (>60%) reported 1 or more non injection site (systemic) AE.

The proportions of children and adults who experienced 1 or more AEs from the second vaccination visit to Day 28 after the second vaccination were generally comparable across intervention groups and AE categories with the exception of injection-site AEs, which were higher in the 2-dose V920 group compared with the 1-dose V920 and placebo groups.

The proportions of children and adults who experienced a SAE were low and comparable for the pooled V920 and placebo groups from the first vaccination to the end of the base study. No participants discontinued from study intervention due to an AE or SAE.

Five children (3 in the 1-dose V920 group, 2 in the placebo group) and 4 adults (3 in the 1-dose V920 group, 1 in the placebo group) died during the study. None of the SAEs or deaths were considered related to study intervention by the investigator.

Summary of AEs in children compared with adults

In the pooled V920 group after the first vaccination, the proportion of children who experienced 1 or more AEs was higher than adults mainly due to a higher proportions of children with injection-site AEs compared with adults (17.7% difference [95% CI: 12.4, 23.0]). The proportions of children with non-injection site AEs and non-serious AEs were also higher compared with adults.

The AE profiles for children and adults in the 2-dose V920 group after the second vaccination were generally comparable.

Table 31 Adverse event summary (First Vaccination Visit to Day 28 After First Vaccination) (All Participants as Treated – Protocol Version 4) (Children)

	V920 1 Dose		V920 2 Dose		Pooled V920[b]		Placebo[c]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	410		198		608		388	
with one or more adverse events	349	(85.1)	169	(85.4)	518	(85.2)	259	(66.8)
injection-site	191	(46.6)	74	(37.4)	265	(43.6)	51	(13.1)
non-injection-site	335	(81.7)	162	(81.8)	497	(81.7)	246	(63.4)
with no adverse event	61	(14.9)	29	(14.6)	90	(14.8)	129	(33.2)
with non-serious adverse events	349	(85.1)	169	(85.4)	518	(85.2)	259	(66.8)
with serious adverse events	0	(0.0)	1	(0.5)	1	(0.2)	1	(0.3)
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)
discontinued vaccine due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious 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. Relatedness was only collected for serious adverse events.
[b] Pooled V920=V920 1 dose or 2 dose.
[c] Placebo=0.5- and 1.0-mL placebo groups.

Table 32 Adverse Event Summary (First Vaccination Visit to Day 28 After First Vaccination) (All Participants as Treated – Protocol Version 4) (Adults)

	V920 1 Dose		V920 2 Dose		Pooled V920[b]		Placebo[c]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	405		187		592		412	
with one or more adverse events	309	(76.3)	138	(73.8)	447	(75.5)	270	(65.5)
injection-site	106	(26.2)	47	(25.1)	153	(25.8)	37	(9.0)
non-injection-site	296	(73.1)	135	(72.2)	431	(72.8)	263	(63.8)
with no adverse event	96	(23.7)	49	(26.2)	145	(24.5)	142	(34.5)
with non-serious adverse events	309	(76.3)	138	(73.8)	447	(75.5)	270	(65.5)
with serious adverse events	1	(0.2)	0	(0.0)	1	(0.2)	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)
discontinued vaccine due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious 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. Relatedness was only collected for serious adverse events.
[b] Pooled V920=V920 1 dose or 2 dose.
[c] Placebo=0.5- and 1.0-mL placebo groups.
AEs with an outcome of death were not reported for 2 participants.

Both injection-site reactions and targeted symptoms were solicited in this study. All solicited injection-site and systemic AEs were collected regardless of grade and were considered related to study intervention per protocol.

The most commonly reported AEs for children and adults were solicited injection-site AEs and solicited systemic AEs. The majority of participants in the pooled V920 and placebo groups for children and adults experienced 1 or more solicited injection-site AEs or solicited systemic AEs from Day 1 to Day 28 after the first vaccination. Lower proportions of children and adults in the 2-dose V920 group and placebo group reported 1 or more solicited AEs from the Day 1 visit to the Month 1 visit after the second vaccination.

Solicited Injection-site Adverse Events (injection-site reaction)

Less than half of children and adults reported solicited injection-site AEs from the Day 1 visit to the Day 28 visit after the first vaccination. Injection-site AEs were reported for a higher proportion of participants in the pooled V920 group compared with the placebo group for both children and adults. In the pooled V920 group, solicited injection-site AEs were reported more frequently for children compared with adults.

The proportions of participants in the 2-dose V920 group with solicited injection-site AEs from Day 1 after the second vaccination to Month 1 after the second vaccination (20.7% children, 16.0% adults) were lower as compared with after first vaccination (37.4% children, 25.1% adults) but higher compared with placebo (8.5% children, 8.3% adults).

Injection-site pain was the most frequently reported injection-site AE for both children and adults and was reported more frequently for children compared with adults.

Injection-site pain was reported for 41.6% of children and 21.5% of adults in the pooled V920 group from the first vaccination visit to Day 28 after the first vaccination visit. Most AEs of injection-site pain were reported in the first 7 days after the first vaccination visit for both children and adults. The highest frequency of reported injection-site pain in children during this time period based on daily contacts was 32.6% for the pooled V920 group and 6.7% for the placebo group at the Day 1 visit. At the Day 7 visit, injection-site pain was reported for 18.4% of children in the pooled V920 group and 3.4% in the placebo group. At the Day 7 visit for adults (retrospective since the first vaccination visit), injection-site pain was reported for 18.4% in the pooled V920 group and 2.4% in the placebo group.

Injection-site pain was reported less frequently in the 2-dose V920 group after the second vaccination compared with after first vaccination.

Solicited Systemic Adverse Events (targeted symptoms)

The following solicited systemic AEs were collected as one line item in the CRF and were reported as a single term in the solicited systemic AE tables in this Summary of Clinical Safety:

- "Reduced activity, somnolence, fatigue" are reported as the term "somnolence".
- "Skin lesions (macules, papules, purpura, petechiae)" are reported as the term "skin lesion".
- "Irritability/fussiness" are reported as the term "irritability".

After First Vaccination

The proportions of children and adults with solicited systemic AEs were higher for the pooled V920 group compared with the placebo group from the Day 1 visit to the Day 28 visit after the first vaccination. The most commonly (>20%) reported solicited systemic AEs in children were pyrexia, headache, somnolence, and decreased appetite. In adults, headache, pyrexia, myalgia, and somnolence. For the individual events in children and adults, the proportions of participants were comparable across intervention groups with the exception of pyrexia, headache, somnolence, and myalgia, which were reported with a higher incidence in V920 groups compared with placebo. Overall, solicited systemic AEs were reported most frequently at the Day 7 visit in children (59.0% pooled V920 group, 41.2% placebo group) and adults (65.5% pooled V920 group, 43.4% placebo group).

After Second Vaccination

Solicited systemic AEs were reported less frequently after the second vaccination compared with the first vaccination for children and adults. The incidence of solicited systemic AEs in the 2 dose V920 group was comparable with the placebo group for both children and adults after the second vaccination. The most

commonly (>20%) reported solicited systemic AEs in the 2-dose V920 group for children were pyrexia and headache (with comparable incidences in the placebo group). Only the solicited systemic AE of headache was reported at an incidence >20% in the 2-dose group for adults (with comparable incidence in the placebo group).

Table 33 Participants with Solicited Targeted Symptoms and Solicited Injection Site Adverse Events (Incidence > 0% in One or More Vaccination Groups) (Day 1 Visit to Day 28 Visit After First Vaccination) (All Participants as Treated – Protocol Version 4) (Children)

	V920 1 Dose		V920 2 Dose		Pooled V920[a]		Placebo[b]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	410		198		608		388	
with one or more solicited adverse events	350	(85.4)	169	(85.4)	519	(85.4)	263	(67.8)
with no solicited adverse events	60	(14.6)	29	(14.6)	89	(14.6)	125	(32.2)
Injection site reactions	**191**	**(46.6)**	**74**	**(37.4)**	**265**	**(43.6)**	**51**	**(13.1)**
Injection site erythema	1	(0.2)	2	(1.0)	3	(0.5)	3	(0.8)
Injection site pain	182	(44.4)	71	(35.9)	253	(41.6)	44	(11.3)
Injection site pruritus	20	(4.9)	5	(2.5)	25	(4.1)	1	(0.3)
Injection site swelling	13	(3.2)	5	(2.5)	18	(3.0)	9	(2.3)
Targeted Symptoms	**336**	**(82.0)**	**162**	**(81.8)**	**498**	**(81.9)**	**251**	**(64.7)**
Abdominal pain	65	(15.9)	34	(17.2)	99	(16.3)	47	(12.1)
Arthralgia	33	(8.0)	9	(4.5)	42	(6.9)	14	(3.6)
Chills	61	(14.9)	27	(13.6)	88	(14.5)	44	(11.3)
Crying	27	(6.6)	12	(6.1)	39	(6.4)	9	(2.3)
Decreased appetite	94	(22.9)	48	(24.2)	142	(23.4)	54	(13.9)
Diarrhoea	22	(5.4)	13	(6.6)	35	(5.8)	24	(6.2)
Dizziness	45	(11.0)	15	(7.6)	60	(9.9)	23	(5.9)

	V920 1 Dose		V920 2 Dose		Pooled V920[a]		Placebo[b]	
	n	(%)	n	(%)	n	(%)	n	(%)
Targeted Symptoms	**336**	**(82.0)**	**162**	**(81.8)**	**498**	**(81.9)**	**251**	**(64.7)**
Headache	195	(47.6)	83	(41.9)	278	(45.7)	122	(31.4)
Hyperhidrosis	14	(3.4)	2	(1.0)	16	(2.6)	7	(1.8)
Irritability	10	(2.4)	3	(1.5)	13	(2.1)	1	(0.3)
Joint swelling	2	(0.5)	1	(0.5)	3	(0.5)	2	(0.5)
Mouth ulceration	7	(1.7)	8	(4.0)	15	(2.5)	2	(0.5)
Myalgia	72	(17.6)	24	(12.1)	96	(15.8)	20	(5.2)
Nausea	33	(8.0)	10	(5.1)	43	(7.1)	18	(4.6)
Pyrexia	255	(62.2)	123	(62.1)	378	(62.2)	150	(38.7)
Screaming	7	(1.7)	4	(2.0)	11	(1.8)	2	(0.5)
Skin lesion	22	(5.4)	8	(4.0)	30	(4.9)	32	(8.2)
Somnolence	102	(24.9)	41	(20.7)	143	(23.5)	49	(12.6)
Vomiting	41	(10.0)	17	(8.6)	58	(9.5)	28	(7.2)

Every participant is counted a single time for each applicable row and column.
[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=0.5- and 1.0-mL placebo groups.

Table 34 Participants with Solicited Targeted Symptoms and Solicited Injection Site Adverse Events (Incidence > 0% in One or More Vaccination Groups) (Day 1 Visit to Day 28 Visit After First Vaccination) (All Participants as Treated – Protocol Version 4) (Adults)

	V920 1 Dose		V920 2 Dose		Pooled V920[a]		Placebo[b]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	405		187		592		412	
with one or more solicited adverse events	312	(77.0)	140	(74.9)	452	(76.4)	272	(66.0)
with no solicited adverse events	93	(23.0)	47	(25.1)	140	(23.6)	140	(34.0)
Injection site reactions	**106**	**(26.2)**	**47**	**(25.1)**	**153**	**(25.8)**	**37**	**(9.0)**
Injection site erythema	4	(1.0)	4	(2.1)	8	(1.4)	10	(2.4)
Injection site pain	90	(22.2)	37	(19.8)	127	(21.5)	17	(4.1)
Injection site pruritus	10	(2.5)	3	(1.6)	13	(2.2)	6	(1.5)
Injection site swelling	14	(3.5)	8	(4.3)	22	(3.7)	12	(2.9)
Targeted Symptoms	**301**	**(74.3)**	**137**	**(73.3)**	**438**	**(74.0)**	**265**	**(64.3)**
Abdominal pain	56	(13.8)	21	(11.2)	77	(13.0)	46	(11.2)
Arthralgia	78	(19.3)	32	(17.1)	110	(18.6)	44	(10.7)
Chills	69	(17.0)	30	(16.0)	99	(16.7)	35	(8.5)
Decreased appetite	62	(15.3)	28	(15.0)	90	(15.2)	39	(9.5)
Diarrhoea	14	(3.5)	6	(3.2)	20	(3.4)	14	(3.4)
Dizziness	48	(11.9)	10	(5.3)	58	(9.8)	34	(8.3)
Headache	228	(56.3)	98	(52.4)	326	(55.1)	179	(43.4)

	V920 1 Dose		V920 2 Dose		Pooled V920[a]		Placebo[b]	
	n	(%)	n	(%)	n	(%)	n	(%)
Targeted Symptoms	**301**	**(74.3)**	**137**	**(73.3)**	**438**	**(74.0)**	**265**	**(64.3)**
Hyperhidrosis	3	(0.7)	5	(2.7)	8	(1.4)	4	(1.0)
Joint swelling	3	(0.7)	1	(0.5)	4	(0.7)	0	(0.0)
Mouth ulceration	10	(2.5)	3	(1.6)	13	(2.2)	2	(0.5)
Myalgia	120	(29.6)	55	(29.4)	175	(29.6)	65	(15.8)
Nausea	40	(9.9)	16	(8.6)	56	(9.5)	26	(6.3)
Pyrexia	164	(40.5)	68	(36.4)	232	(39.2)	94	(22.8)
Skin lesion	12	(3.0)	3	(1.6)	15	(2.5)	10	(2.4)
Somnolence	102	(25.2)	49	(26.2)	151	(25.5)	56	(13.6)
Vomiting	18	(4.4)	8	(4.3)	26	(4.4)	5	(1.2)

Every participant is counted a single time for each applicable row and column.
[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=0.5- and 1.0-mL placebo groups.

Unsolicited adverse events

Only Grade 3 and Grade 4 unsolicited AEs were reported during the study. Four participants (2 children and 2 adults) reported a Grade 3 or Grade 4 unsolicited AE:

- One child in the 2-dose V920 group with Grade 4 unilateral blindness. This SAE was considered not related to study intervention by the investigator
- One child in the 2-dose V920 group with Grade 3 insomnia
- One adult in the 1-dose V920 group with Grade 3 hypertension
- One adult in the placebo group with Grade 3 toothache

The MAH confirmed that no cases of vesicular rash were observed in children nor in adults:

Skin lesion was reported for 22 (5.4%) children in the V920 1-Dose group, 8 (4.0%) children in the V920 2-dose group, and 32 (8.2%) children in the placebo group. Skin lesion was reported for 12 (3.0%) adults in the V920 1-Dose group, 3 (1.6%) adults in the V920 2-dose group, and 10 (2.4%) adults in the placebo group.

Joint swelling was reported for 2 (0.5%) children in the V920 1-Dose group, 1 (0.5%) child in the V920 2-dose group, and 2 (0.5%) children in the placebo group. Joint swelling was reported for 3 (0.7%) adults in the V920 1-Dose group, 1 (0.5%) adult in the V920 2-dose group, and 0 (0.0%) adults in the placebo group.

Serious adverse event/deaths/other significant events

Deaths

Nine deaths were reported, and were considered not related to the study intervention by the investigator:

Children (n=5):

- 1-dose V920 group: drowning (n=1); "death", with primary cause of death reported as pyrexia (n=1); and "death", with primary cause of death reported as unknown (n=1)
- Placebo group: sickle cell anaemia with crisis (n=1); and "death", with primary cause of death reported as unknown (n=1)

Adults (n=4):

- 1-dose V920 group: sepsis (n=1), HIV infection (n=1), and appendicitis (n=1)
- Placebo group: anaemia (n=1)

The primary cause of death was unknown for 1 child in the 1-dose V920 group (Day 164 after the second vaccination, with placebo) and 1 child in the placebo group (Day 51 after the first vaccination). The death

reported with primary cause of pyrexia for 1 child in the 1-dose V920 group occurred on Day 110 after the second vaccination, with placebo. The relative days of death were remote from the day of vaccination with V920 and past the postvaccination time period for reporting of AEs. These participants did not experience any vaccine-related non-serious AEs during the time period in which they were observed at the healthcare centres.

Two adult participants randomised to the 1-dose V920 group under Protocol Version 4.0 did not have an outcome of "fatal" recorded for the SAE resulting in death at the time of data entry and therefore, were not included in AE summary tables. The causes of death for these participants were reported in the Death Declaration CRFs as HIV infection and appendicitis.

Other SAE

The proportions of children and adults who experienced one or more SAEs from the first vaccination to the end of the base study were low and comparable for the pooled V920 and placebo groups.

SAEs reported for children and adults from the first vaccination to the end of the base study were mostly single events with the exception of death, appendicitis, malaria, and ill-defined disorder (1 participant in the 1-dose V920 group with polycystic ovary and appendicitis; 1 participant in the 2-dose V920 group with severe malaria, anaemia, prostration, and hypoglycaemia; 1 participant in the placebo group with hematoma of soft tissue). Two participants had laboratory-confirmed malaria requiring hospitalisation.

After the second vaccination, the proportions of children and adults who experienced SAEs were comparable for the 2-dose V920 and placebo groups.

No participants had an SAE considered by the investigator to be vaccine related and no SAEs led to discontinuation from the study. With the exception of a single event of pyrexia in a child in the 1-dose V920 group, all of the SAEs were unsolicited events.

The assessment of SAEs for the protocol version 4.0 and 3.0 population showed no emergent pattern of SAEs after participants were administered either dose of V920 during the study.

Table 35 Participants with SAE (Incidence > 0% in one or more vaccination groups) (First Vaccination to End of Base Study) (All Participants as Treated – Protocol Version 4) (Children)

	V920 1 Dose		V920 2 Dose		Pooled V920[a]		Placebo[b]	
	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**4**	**(1.0)**	**1**	**(0.5)**	**5**	**(0.8)**	**1**	**(0.3)**
Ill-defined disorder	0	(0.0)	1	(0.5)	1	(0.2)	0	(0.0)
Pyrexia	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)
Infections and infestations	**2**	**(0.5)**	**1**	**(0.5)**	**3**	**(0.5)**	**4**	**(1.0)**
Appendicitis	1	(0.2)	0	(0.0)	1	(0.2)	2	(0.5)
Malaria	0	(0.0)	1	(0.5)	1	(0.2)	1	(0.3)
Pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Typhoid fever	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)
Injury, poisoning and procedural complications	**1**	**(0.2)**	**2**	**(1.0)**	**3**	**(0.5)**	**2**	**(0.5)**
Capsular block syndrome	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)
Clavicle fracture	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Eye injury	0	(0.0)	1	(0.5)	1	(0.2)	0	(0.0)
Humerus fracture	0	(0.0)	1	(0.5)	1	(0.2)	0	(0.0)
Radius fracture	0	(0.0)	1	(0.5)	1	(0.2)	0	(0.0)
Venom poisoning	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Musculoskeletal and connective tissue disorders	**1**	**(0.2)**	**0**	**(0.0)**	**1**	**(0.2)**	**0**	**(0.0)**
Back pain	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)
Pregnancy, puerperium and perinatal conditions	**1**	**(0.2)**	**0**	**(0.0)**	**1**	**(0.2)**	**0**	**(0.0)**
Abortion incomplete	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)

Every participant is counted a single time for each applicable row and column.
[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=0.5- and 1.0-mL placebo groups.

Table 36 Participants with Serious Adverse Events (Incidence > 0% in One or More Vaccination Groups) (First Vaccination to End of Base Study) (All Participants as Treated – Protocol Version 4) (Adults)

	V920 1 Dose		V920 2 Dose		Pooled V920[a]		Placebo[b]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	405		187		592		412	
with one or more serious adverse events	6	(1.5)	1	(0.5)	7	(1.2)	5	(1.2)
with no serious adverse events	399	(98.5)	186	(99.5)	585	(98.8)	407	(98.8)
Blood and lymphatic system disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**
Anaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Gastrointestinal disorders	**1**	**(0.2)**	**0**	**(0.0)**	**1**	**(0.2)**	**0**	**(0.0)**
Abdominal pain upper	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)
General disorders and administration site conditions	**1**	**(0.2)**	**0**	**(0.0)**	**1**	**(0.2)**	**1**	**(0.2)**
Ill-defined disorder	1	(0.2)	0	(0.0)	1	(0.2)	1	(0.2)
Infections and infestations	**4**	**(1.0)**	**1**	**(0.5)**	**5**	**(0.8)**	**3**	**(0.7)**
Appendicitis	1	(0.2)	1	(0.5)	2	(0.3)	2	(0.5)
Cellulitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
HIV infection	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)
Peritonitis	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)
Infections and infestations	**4**	**(1.0)**	**1**	**(0.5)**	**5**	**(0.8)**	**3**	**(0.7)**
Pulmonary tuberculosis	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)
Sepsis	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)
Injury, poisoning and procedural complications	**1**	**(0.2)**	**0**	**(0.0)**	**1**	**(0.2)**	**1**	**(0.2)**
Head injury	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Humerus fracture	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)
Pregnancy, puerperium and perinatal conditions	**1**	**(0.2)**	**0**	**(0.0)**	**1**	**(0.2)**	**0**	**(0.0)**
Ectopic pregnancy	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)

Every participant is counted a single time for each applicable row and column.
[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=0.5- and 1.0-mL placebo groups.

V920 shedding in children (Study V920-016 PREVAC)

V920 shedding was assessed at baseline and Days 7, 14, 28, 56 (day of second vaccination), and 63, and month 3. Overall, 31.7% (19/60) of children in the pooled V920 group shed vaccine virus after the first vaccination under protocol version 4.0. Submitted data indicate that in children aged 3-17 years, shedding peaked between Day 7 and Day 14 following administration of the first dose of V920 both for protocol version 3.0 and 4.0, with no shedding detected in either the 1- or 2-dose V920 groups at Day 56. No shedding was observed after the second vaccination (Day 56) in the children in this subset who received 2 doses of V920 (n=21).

The results observed for the subgroups of children 3 to <12 and 12 to 17 years of age were comparable with those observed for children overall. No shedding was detected in children 1 to <3 years of age. Numbers of participants aged 1 to <3 years included in the shedding substudy were as follow:

Under protocol version 4.0:

- 1-dose V920 group: 2 participants (1 year: n=0; 2 years: n=2)
- 2-dose V920 group: 3 participants (1 year: n=1; 2 years: n=2)
- Placebo group: 3 participants (1 year: n=1; 2 years: n=2)

Under protocol version 3.0:

- 1-dose V920 group: 1 participant (1 year: n=0; 2 years: n=1)
- 2-dose V920 group: 0 participants (1-2 years, n=0)
- Placebo group: 0 participants (1-2 years, n=0)

Quantitative RT-PCR data and individual trajectories of copies/mL over time indicate that in children aged 3-17 years, shedding peaked at a mean of Day 8.7 and 10.8 post dose 1 for the V920 1-dose and 2-dose groups under protocol version 4.0. Under protocol version 3.0, shedding peaked at a mean of Day 9.7 and Day 11.0 post dose 1 for the V920 1-dose and 2-dose groups, respectively.

Table 37: Shedding of VSV-ZEBOV Over Time (All Participants as Treated – Protocol Version 4) (Children)

Assay Time Point	V920 1 Dose (N=410) Percent (m/n) [95% CI]	V920 2 Dose (N=198) Percent (m/n) [95% CI]	Pooled V920[a] (N=608) Percent (m/n) [95% CI]	Placebo[b] (N=388) Percent (m/n) [95% CI]
At any time	28.2 (11/39) [15.0%, 44.9%]	38.1 (8/21) [18.1%, 61.6%]	31.7 (19/60) [20.3%, 45.0%]	0.0 (0/36) [0.0%, 9.7%]
Day 0	2.6 (1/39) [0.1%, 13.5%]	0.0 (0/21) [0.0%, 16.1%]	1.7 (1/60) [0.0%, 8.9%]	0.0 (0/35) [0.0%, 10.0%]
Day 7	23.1 (9/39) [11.1%, 39.3%]	28.6 (6/21) [11.3%, 52.2%]	25.0 (15/60) [14.7%, 37.9%]	0.0 (0/35) [0.0%, 10.0%]
Day 14	13.2 (5/38) [4.4%, 28.1%]	14.3 (3/21) [3.0%, 36.3%]	13.6 (8/59) [6.0%, 25.0%]	0.0 (0/35) [0.0%, 10.0%]
Day 28	2.6 (1/38) [0.1%, 13.8%]	0.0 (0/21) [0.0%, 16.1%]	1.7 (1/59) [0.0%, 9.1%]	0.0 (0/35) [0.0%, 10.0%]
Day 56	0.0 (0/39) [0.0%, 9.0%]	0.0 (0/21) [0.0%, 16.1%]	0.0 (0/60) [0.0%, 6.0%]	0.0 (0/35) [0.0%, 10.0%]
Day 63	0.0 (0/39) [0.0%, 9.0%]	0.0 (0/21) [0.0%, 16.1%]	0.0 (0/60) [0.0%, 6.0%]	0.0 (0/35) [0.0%, 10.0%]
Month 3	0.0 (0/39) [0.0%, 9.0%]	0.0 (0/21) [0.0%, 16.1%]	0.0 (0/60) [0.0%, 6.0%]	0.0 (0/35) [0.0%, 10.0%]

Percent=m/n and represents proportion of participants with shedding > 0.
[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=0.5-and 1.0-mL placebo groups.
N=number of participants with serology data at one or more timepoints according to the treatment to which they were randomized.
n=number of participants contributing to the analysis. m=number of participants with shedding. CI=confidence interval.

Laboratory findings

No clinically significant changes in biochemical markers or complete blood count over time were observed for children in any of the study intervention groups.

Vital signs, physical findings and other observations

Solicited maximum temperature

Body temperature measurements (temporal) were obtained from children at daily contacts and study visits and adults at study visits. Participants did not record daily temperatures outside of the scheduled visits for children and adults and daily contacts for children.

Overall, the majority (94.3%) of children and most (99.6%) adults had a maximum body temperature of <38.0°C from the first vaccination visit to Day 28 after the first vaccination. The remainder experienced at least one occurrence of elevated body temperature (maximum body temperature ≥38.0°C) after the first vaccination. For both children and adults, the proportions of participants with elevated body temperature were generally similar for the pooled V920 and placebo groups.

The proportion of participants in the pooled V920 group with elevated body temperature (maximum body temperature ≥38.0°C) after the first vaccination was higher for children compared with adults (7.4% vs 0.5%). The proportion of participants with elevated body temperatures in the 2-dose V920 group was lower after the second vaccination compared with the first vaccination (1.0% children, 0.0% adults).

In the pooled V920 group, 10.9% of children who took an antipyretic and 2.7% of children who did not take an antipyretic experienced elevated body temperature (maximum body temperature ≥38.0°C) after the first vaccination.

Participants were queried regarding feverishness since their last visit to determine AEs of pyrexia. The vast majority of AEs of pyrexia (>98%) were Grade 1 or Grade 2.

Table 38 Maximum temperatures (Greater Than or Equal to 38.0°C) First Vaccination Visit to Day 28 Visit After First Vaccination (All Participants as Treated – Protocol Version 4) (Children)

	V920 1 Dose		V920 2 Dose		Pooled V920[a]		Placebo[b]		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	410		198		608		388		996	
without temperature data	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.1)
with temperature data	410	(100.0)	198	(100.0)	608	(100.0)	387	(99.7)	995	(99.9)
Maximum Temperature (Temporal)										
< 38 °C (100.4 °F)	378	(92.2)	185	(93.4)	563	(92.6)	375	(96.9)	938	(94.3)
≥ 38 °C (100.4 °F)	32	(7.8)	13	(6.6)	45	(7.4)	12	(3.1)	57	(5.7)

Percentages for the maximum temperature categories are calculated based on the number of participants with temperature data.
Multiple occurrences of maximum temperature are counted only once.
All measured temperatures were temporal.
[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=0.5- and 1.0-mL placebo groups.

Table 39 Maximum Temperatures (Greater Than or Equal to 38.0°C) First Vaccination Visit to Day 28 Visit After First Vaccination (All Participants as Treated – Protocol Version 4) (Adults)

	V920 1 Dose		V920 2 Dose		Pooled V920[a]		Placebo[b]		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	405		187		592		412		1,004	
without temperature data	6	(1.5)	0	(0.0)	6	(1.0)	3	(0.7)	9	(0.9)
with temperature data	399	(98.5)	187	(100.0)	586	(99.0)	409	(99.3)	995	(99.1)
Maximum Temperature (Temporal)										
< 38 °C (100.4 °F)	397	(99.5)	186	(99.5)	583	(99.5)	408	(99.8)	991	(99.6)
≥ 38 °C (100.4 °F)	2	(0.5)	1	(0.5)	3	(0.5)	1	(0.2)	4	(0.4)

Percentages for the maximum temperature categories are calculated based on the number of participants with temperature data.
Multiple occurrences of maximum temperature are counted only once.
All measured temperatures were temporal.
[a] Pooled V920=V920 1 dose or 2 dose.
[b] Placebo=0.5- and 1.0-mL placebo groups.

Physical examinations in children

There were no clinically meaningful safety-related findings in children as a result of the physical examination assessments (height, weight, and mid-upper arm circumference). The assessments were comparable across intervention groups.

Safety in special populations

Safety analyses were conducted for children based on the following age subgroups: 1 to <3 years, 3 to <12 years, and 12 to 17 years.

Version 4 (main data)

The percentage of subjects with one or more adverse events was 88% in the age category below 3 years, 86% between 3 to 11 years, and 83% in the age category 12 to 17 years of age.

The safety profile in the different age categories was in general comparable apart from pyrexia which was observed more frequently in the youngest age category (1 to 3 years of age: 83% of subjects, 3 to 11 years of age: 65%, 12 to 17 years of age: 48%). But pyrexia was also observed more frequently in the placebo arm in this population (1 to 3 years of age: 67% of subjects, 3 to 11 years of age: 37%, 12 to 17 years of age: 28%).

Only small number of patients did experience a SAE (1 to 3 years of age: 1.1% of subjects, 3 to 11 years of age: 1.9%, 12 to 17 years of age: 2.5%).

Pooled version 3 (supportive data) and 4 (main data)

The percentage of subjects with one or more adverse events was 92.4% in the age category below 3 years, 89.6% between 3 to 11 years, and 81.6% in the age category 12 to 17 years of age.

The safety profile in the different age categories was in general comparable apart from pyrexia which was observed more frequently in the youngest age category (1 to 3 years of age: 87.6% of subjects, 3 to 11 years of age: 70.1%, 12 to 17 years of age: 43.1%). But pyrexia was also observed more frequently in the placebo arm in this population (1 to 3 years of age: 75% of subjects, 3 to 11 years of age: 45.8%, 12 to 17 years of age: 30.6%).

Concerning the solicited events per grade, similar patterns were seen in the different age categories. Only small number of patients did experience a SAE (1 to 3 years of age: 1% of subjects, 3 to 11 years of age: 1.9%, 12 to 17 years of age: 2.3%).

V920 was generally well tolerated by participants in each age subgroup. The AE profiles (in terms of AE categories and frequency) for the subgroups of children were generally consistent with the population of children 1 to 17 years of age with the exception of injection-site AEs in the V920 groups, which were reported less frequently in children 1 to <3 years of age.

The proportions of participants who experienced 1 or more AEs from the first vaccination to the end of the base study were generally comparable for the pooled V920 group and placebo group in children 1 to <3 years of age but higher for the pooled V920 group compared with the placebo group in children 3 to <12 years of age and 12 to 17 years of age. Across age subgroups, the proportions of children with SAEs were low and generally comparable for the pooled V920 and placebo groups; no vaccine-related SAEs, vaccine-related deaths, or discontinuations from study intervention due to an AE were reported. The proportions of participants who died were comparable for the pooled V920 and placebo groups for children 3 to <12 years of age and 12 to 17 years of age; no deaths were reported for children 1 to <3 years of age.

Trends toward higher proportions of participants with injection-site AEs but lower proportions of participants with non-injection-site AEs were observed in the oldest subgroup of children (12 to 17 years of age) compared with the youngest (1 to <3 years of age).

The most commonly (>20% in one or more vaccination groups) reported solicited injection site AE after the first vaccination among the subgroups of children was injection site pain. Injection-site pain was more frequently reported for children 3 to 11 and 12 to 17 years of age than in children 1 to <3 years of age.

The 3 most commonly reported solicited systemic AEs in the pooled V920 group were pyrexia, crying, and decreased appetite for children 1 to <3 years of age; pyrexia, headache, and decreased appetite for children 3 to <12 years of age; and headache, pyrexia, and myalgia for children 12 to 17 years of age. Pyrexia was reported for a higher proportion of children 1 to <3 years of age compared with children 3 to <12 and 12 to 17 years of age.

Table 40 Adverse Event Summary First Vaccination to End of Base Study (All Participants as Treated – Protocol Version 4.0) (Subgroups of Children)

Participants	Category	V920 1 Dose n (%)	V920 2 Dose n (%)	Pooled V920[a] n (%)	Placebo[b] n (%)
Children 1 to <3 Years of Age	Participants in population	58	37	95	60
	with ≥1 AEs	51 (87.9)	36 (97.3)	87 (91.6)	53 (88.3)
	injection-site	22 (37.9)	9 (24.3)	31 (32.6)	9 (15.0)
	non-injection site	51 (87.9)	35 (94.6)	86 (90.5)	53 (88.3)
	with non-serious AEs	51 (87.9)	36 (97.3)	87 (91.6)	53 (88.3)
	with SAEs	1 (1.7)	0 (0.0)	1 (1.1)	0 (0.0)
	with vaccine-related[c] SAEs	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 vaccine-related[c] AE	0 (0.0	0 (0.0	0 (0.0	0 (0.0
	who discontinued vaccine due to an AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	who discontinued vaccine due to an SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	who discontinued vaccine due to a vaccine-related[c] SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Children 3 to <12 Years of Age	Participants in population	214	96	310	205
	with ≥1 AE	196 (91.6)	85 (88.5)	281 (90.6)	167 (81.5)
	injection-site	107 (50.0)	41 (42.7)	148 (47.7)	31 (15.1)
	non-injection site	194 (90.7)	84 (87.5)	278 (89.7)	160 (78.0)
	with non-serious AE	196 (91.6)	85 (88.5)	281 (90.6)	167 (81.5)
	with SAE	4 (1.9)	2 (2.1)	6 (1.9)	1 (0.5)
	with vaccine-related[c] SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	who died	2 (0.9)	0 (0.0)	2 (0.6)	0 (0.0)
	who died due to vaccine-related[c] AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	who discontinued vaccine due to an AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	who discontinued vaccine due to an SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	who discontinued vaccine due to a vaccine-related[c] SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Children 12 to 17 Years of Age	Participants in population	138	65	203	123
	with ≥1 AE	117 (84.8)	59 (90.8)	176 (86.7)	90 (73.2)
	injection-site	73 (52.9)	40 (61.5)	113 (55.7)	28 (22.8)
	non-injection site	108 (78.3)	56 (86.2)	164 (80.8)	86 (69.9)
	with non-serious AE	117 (84.8)	59 (90.8)	176 (86.7)	89 (72.4)
	with SAE	4 (2.9)	1 (1.5)	5 (2.5)	7 (5.7)
	with vaccine-related[c] SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	who died	1 (0.7)	0 (0.0)	1 (0.5)	2 (1.6)
	who died due to vaccine-related[c] AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	who discontinued vaccine due to an AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	who discontinued vaccine due to an SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	who discontinued vaccine due to a vaccine-related[c] SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AE=adverse event; SAE=serious adverse event

[a] Pooled V920=V920 1 dose or 2 dose.

[b] Placebo=0.5- and 1.0-mL placebo groups

[c] Determined by the investigator to be related to the vaccine. Relatedness was only collected for serious adverse events.

Table 41 Participants with Solicited Adverse Events (Incidence ≥20% in One or More Vaccination Groups) (Day 1 Visit to Day 28 Visit After First Vaccination) (All Participants as Treated – Protocol Version 4.0) (Subgroups of Children)

Participants	Solicited Adverse Event	V920 1 Dose n (%)	V920 2 Dose n (%)	Pooled V920[a] n (%)	Placebo[b] n (%)
Children 1 to <3 Years of Age	Participants in population	58	37	95	60
	with ≥1 solicited AEs	50 (86.2)	34 (91.9)	84 (88.4)	48 (80.0)
	Pyrexia	47 (81.0)	32 (86.5)	79 (83.2)	40 (66.7)
	Crying	21 (36.2)	8 (21.6)	29 (30.5)	4 (6.7)
	Decreased appetite	15 (25.9)	11 (29.7)	26 (27.4)	9 (15.0)\
	Injection-site pain	19 (32.8)	6 (16.2)	25 (26.3)	5 (8.3)
	Somnolence	13 (22.4)	6 (16.2)	19 (20.0)	5 (8.3)
	Diarrhea	12 (20.7)	6 (16.2)	18 (18.9)	10 (16.7)
Children 3 to <12 Years of Age	Participants in population	214	96	310	205
	with ≥1 solicited AE	188 (87.9)	79 (82.3)	267 (86.1)	142 (69.3)
	Pyrexia	143 (66.8)	58 (60.4)	201 (64.8)	76 (37.1)
	Headache	111 (51.9)	43 (44.8)	154 (49.7)	71 (34.6)
	Injection-site pain	94 (43.9)	28 (29.2)	122 (39.4)	18 (8.8)
	Decreased appetite	48 (22.4)	26 (27.1)	74 (23.9)	27 (13.2)
	Somnolence	45 (21.0)	22 (22.9)	67 (21.6)	20 (9.8)
	Abdominal pain	44 (20.6)	21 (21.9)	65 (21.0)	29 (14.1)
Children 12 to 17 Years of Age	Participants in population	138	65	203	123
	with ≥1 solicited AE	112 (81.2)	56 (86.2)	168 (82.8)	73 (59.3)
	Headache	82 (59.4)	38 (58.5)	120 (59.1)	48 (39.0)
	Pyrexia	65 (47.1)	33 (50.8)	98 (48.3)	34 (27.6)
	Injection-site pain	69 (50.0)	37 (56.9)	106 (52.2)	21 (17.1)
	Myalgia	46 (33.3)	14 (21.5)	60 (29.6)	12 (9.8)
	Somnolence	44 (31.9)	13 (20.0)	57 (28.1)	24 (19.5)
	Decreased appetite	31 (22.5)	11 (16.9)	42 (20.7)	18 (14.6)
	Chills	31 (22.5)	8 (12.3)	39 (19.2)	20 (16.3)

AE=adverse event

[a] Pooled V920=V920 1 dose or 2 dose.

[b] Placebo=0.5- and 1.0-mL placebo groups

Safety related to drug-drug interactions and other interactions

V920 was not administered concomitantly with any other vaccines in the V920-016 study. Therefore, vaccine interactions were not evaluated.

Post marketing experience

As of the PSUR covering the reporting period from 11-May-2021 to 10-Nov-2021, cumulatively, approximately 4800 subjects (non-study) were estimated to have been vaccinated with licensed doses of V920, based on the assumption that every dose released from the licensed dose stockpiles was used in a non-study setting, and each subject received one dose. There were no records of any registration being revoked or withdrawn for safety reasons. During the reporting interval of this PSUR, there were no safety-related updates to the CCSI for V920. It was concluded that overall, the previously established favourable benefit-risk profile for V920 was reconfirmed by the efficacy and safety data that became available during this reporting interval.

There was no published literature that described new and potentially important safety information on Ebola Zaire vaccine.

Using an aggregate data analysis tool, the company safety database was searched for spontaneous reports cumulatively through 31-Jan-2022. A total of 16 spontaneous reports containing 63 events (1 serious, 62 non-serious) were identified.

Table 42 Adverse Events from Spontaneous Reports for V920 Cumulative through 31-Jan-2022

System Organ Class	Preferred Term	Number of Serious Events	Number of Non-Serious Events	Number of Events
Blood and lymphatic system disorders	Leukopenia	0	1	1
	Neutropenia	0	1	1
Gastrointestinal disorders	Diarrhoea	0	2	2
	Nausea	0	2	2
	Vomiting	0	1	1
General disorders and administration site conditions	Adverse drug reaction	0	1	1
	Asthenia	0	6	6
	Chest pain	0	1	1
	Chills	0	2	2
	Fatigue	0	1	1
	Ill-defined disorder	0	1	1
	Injection site pain	0	1	1
	Malaise	0	1	1
	Pyrexia	0	9	9
	Vaccination site pain	0	4	4
	Vaccination site reaction	0	1	1
Investigations	Aspartate aminotransferase increased	0	1	1
Musculoskeletal and connective tissue disorders	Arthralgia	0	3	3
	Myalgia	0	6	6
Nervous system disorders	Dizziness	0	1	1
	Headache	0	10	10
	Muscle contractions involuntary	0	1	1
	Tremor	0	1	1
Respiratory, thoracic and mediastinal disorders	Dyspnoea	0	1	1
	Hypoxia	1	0	1
Skin and subcutaneous tissue disorders	Hyperhidrosis	0	1	1
	Rash	0	1	1
Vascular disorders	Hypotension	0	1	1
Grand total	**Grand total**	**1**	**62**	**63**

There were 7 female and 8 male subjects in the 16 cases, with gender information not provided in 1 case. Subject age (available in 14 cases) ranged from 28 to 46 years.

The only serious event (PT hypoxia) was from literature report which included 5 subjects who received V920 as post-exposure prophylaxis after a potential exposure to EBOV in West Africa. Limited details were provided concerning this event (including no information on time-to-onset, clinical course, medical history, or concomitant medications), which precludes meaningful assessment.

Of the 62 non-serious events, event outcome was reported as recovering/recovered in 59 events, not recovered for 1 event, and unknown for 2 events. 41 of the 62 non-serious events (PT nausea, chills, fatigue, injection-site pain, pyrexia, vaccination-site pain, vaccination-site reaction, arthralgia, myalgia, headache, rash, hyperhidrosis) are listed or consistent with listed events in the CCSI for V920. Of the remaining 21 events, 2 events (which were reported in the same case) with the PT ADR and ill-defined disorder are non-specific and provide limited information which precludes meaningful assessment. Conclusions from the review of the cases containing the remaining 19 non-serious events were that there was insufficient information to assess a causal relationship between the events and V920.

An analysis of post-marketing data received from spontaneous sources did not identify any cases in paediatric subjects. No new safety issues were identified from this review. The MAH will continue to monitor the safety of V920 through routine pharmacovigilance.

2.5.1. Discussion on clinical safety

Assessment of paediatric data on clinical safety

As presented by the MAH, data obtained with protocol version 4.0 (approved dose) are mainly shown in this report while data obtained with protocol version 3.0 are considered as supportive.

For adults and children, the MAH pooled the data after dose 1 (1st group) with data after dose 1 in the 2-dose group (2nd group) as the approved posology is only one dose (protocol version 4.0). This is considered acceptable and therefore, the data after 2 doses of V920 are not discussed in this report.

The safety profile in the different age categories is in general comparable apart from pyrexia which was observed more frequently in the youngest age category (1 to 3 years of age). But pyrexia was also observed more frequently in the placebo arm in this population.

The proportions of children and adults who experienced an SAE were low and comparable for the pooled V920 and placebo groups from the first vaccination to the end of the base study. No participants discontinued from study intervention due to an AE or SAE. Five children (3 in the 1-dose V920 group, 2 in the placebo group) and 4 adults (3 in the 1 dose V920 group, 1 in the placebo group) died during the study. None of the SAEs or deaths were considered related to study intervention by the investigator.

Overall, no differences were identified between the safety data with protocol version 4.0 compared to the pooled version 3.0 (supportive data) and version 4.0.

Shedding

The aim of the saliva shedding substudy was to estimate the proportion of children who have detectable vaccine virus by qRT-PCR but also to quantify vaccine virus levels shed after a prime and a boost vaccine dose. The MAH only submitted data on the proportion of tested participants with shedding > 0 and was requested to also submit quantitative data and individual trajectories of copies/mL over time, with data stratified by age and presented separately for protocol versions 3.0 and 4.0.

Under protocol version 4.0, a total of 5 participants aged 1 to <3 years were randomised to V920 (1 or 2 doses) and under version 3.0, just one participant. Given the limited sample size, no conclusions can be drawn for this age category and data from the V920-014 trial should be submitted when available **(REC)**.

In study V920-007, V920 shedding was detected in the saliva of a higher proportion of school-age children and adolescents compared to adults in general (all studies).

At Day 7, V920 RNA was detectable in saliva in 35% of school-age children and in 88% of adolescents. The maximum shedding value was 7x104 copies/mL in adolescent saliva. The proportion of V920 positive saliva samples at Day 7 is lower in the V920-016 study. The MAH hypotheses that this difference could be the result of a lower age range for children in V920-016 (1 to 17 years of age) compared with V920-007 (6 to 17 years of age) and/or differences in the assays used may have contributed to the different results obtained. Difference might also be due to the limited sample sizes. In addition, in one vaccinated participant of protocol version 3.0, 331284 copies/mL of vaccine virus were detected on Day 7. This was classified as anomalous by the MAH. It is however noted that this higher value is observed for a child of 9 years of age (and not an adolescent, as observed for study V920-007).

The proposed statement in SmPC section 4.4. related to viremia and viral shedding with the changes proposed is accepted. However, a special warning was added for parents or caregivers of young vaccinees to minimise exposure to shed vaccine virus. See section 2.7 (update of the product information) to see the complete details on transmission and transmission to animals and livestock.

Viral shedding/secondary transmission to close contacts, particularly immunocompromised hosts is an important potential risk in the RMP. The V920-015 ACHIV trial, conducted in Canada, Burkina Faso, and Senegal will study the safety and tolerability (including viral shedding) of V920 in HIV-positive adults and adolescents 13 to 70 years of age. Moreover, another trial, EBOLAPED (not specified in RMP), will evaluate the safety and immunogenicity of the rVSVΔG-ZEBOV-GP EBOV vaccine candidate in healthy children aged 1 to 12 years and in their adults and/or children relatives living in Lambaréné, Gabon. The available results on the shedding of EBOLAPED should be provided **(REC)**.

2.5.2. Conclusions on clinical safety

The overall safety profile in the paediatric population is in accordance with the safety data in adults after one dose of V920. No new safety signals were identified.

In the V920 pooled group, in general the most common injection-site AE and systemic AE were reported within 7 days after vaccination and were mild to moderate in intensity. The safety profile in the different age categories was in general comparable apart from pyrexia, which was observed more frequently in the youngest age category (1 to 3 years of age). However, pyrexia was more frequent in the placebo arm in this population.

The number of subjects in the age category from 1 to 3 years of age was rather limited: 41 children between 1 and 2 years of age and 54 children between 2 and 3 years of age vaccinated with V920 (total of 95 children 1-3 as expected), versus 23 children between 1 and 2 years of age and 37 children between 2 and 3 years of age vaccinated with placebo (total of 60 children 1-3 as expected).

Recommendations (REC) are considered necessary to address issues related to safety (see section 3.8 – Conclusions).

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC

and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 2.0 with the following content:

Safety concerns

Table 43: 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

Pharmacovigilance plan

Table 44: On-Going and Planned Additional Pharmacovigilance Activities

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable.				
Category 3 - Required additional pharmacovigilance activities				
V920-015 ACHIV Ongoing	1) To evaluate the safety and tolerability of V920 in HIV-infected adults and adolescents. 2) To evaluate the immunogenicity of V920 via ZEBOV- specific antibody responses induced by V920 in HIV-infected adults and adolescents.	-Exposure in HIV-infected individuals -Viral shedding	Final report (Clinical Study Report)	Target: Q2 2024

Table 44: On-Going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
V920-EAP5 Amendment #1 Ongoing	Primary Objectives: 1) To evaluate the safety of the V920 vaccine by following SAEs for 21 days for all participants. Secondary Objectives: 1) To summarize the cumulative incidence of EVD laboratory-confirmed cases amongst eligible persons after 21 days of monitoring, where a ring vaccination or geographically targeted vaccination strategy has been used. 2) To document the safety of a single dose of V920 vaccine in evaluating the solicited AEs (fever, headaches, tiredness, diarrhoea, vomiting, myalgia, arthralgia and local reactogenicity) for 21 days and the unsolicited AEs during the 21 days of follow-up for all participants.	-Exposure in pregnancy -Exposure in lactation	Final report	Target: 8 months after all data have been transferred to the company and the company database is locked

Risk minimisation measures

Table 45: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Viral shedding/secondary transmission to close contacts, particularly immunocompromised hosts	Special warnings and precautions for use section of the product information. What you need to know before you receive ERVEBO section of the patient information.	Routine pharmacovigilance activities Additional pharmacovigilance activities: Viral shedding: V920-015 African-Canadian Study of HIV-Infected Adults and a Vaccine for Ebola (ACHIV-Ebola)
Exposure during pregnancy	Special warnings and precautions for use and the Fertility, pregnancy and lactation sections of the product information. What you need to know before you receive ERVEBO section of the patient information.	Routine pharmacovigilance activities Additional pharmacovigilance activities: WHO-sponsored trial (V920-EAP5): Compassionate ring vaccination study to evaluate the safety of the Ebola vaccine in the Democratic Republic of the Congo

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Exposure during lactation	Special warnings and precautions for use and the Fertility, pregnancy and lactation sections of the product information. What you need to know before you receive ERVEBO section of the patient information.	Routine pharmacovigilance activities Additional pharmacovigilance activities: WHO-sponsored trial (V920-EAP5): Compassionate ring vaccination study to evaluate the safety of the Ebola vaccine in the Democratic Republic of the Congo
Exposure in HIV-infected individuals	Special warnings and precautions for use section of the product information. What you need to know before you receive ERVEBO section of the patient information.	Routine pharmacovigilance activities Additional pharmacovigilance activities: V920-015 African-Canadian Study of HIV-Infected Adults and a Vaccine for Ebola (ACHIV-Ebola)

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.3 of the SmPC have been updated. Changes related to SmPC sections 4.1, 4.2 and 4.4 are summarised below (new text in bold and deleted text marked as strikethrough):

Section 4.1

Ervebo is indicated for active immunisation of individuals 1~~8~~ year~~s~~ of age or older to protect against Ebola Virus Disease (EVD) caused by Zaire Ebola virus (see sections 4.2, 4.4 and 5.1).

Section 4.2

Ervebo should be administered by a trained healthcare worker.

Posology

Individuals 1~~8~~ year~~s~~ of age or older: one dose (1 mL) (see section 5.1).

Booster dose
The need **and appropriate timing** for ~~a~~ booster dose**(s)** ~~has~~ **have** not been established. **Current available data are included in section 5.1.**

Paediatric population

The **posology in children 1 to 17 years of age is the same as in adults.** ~~s~~**S**afety, immunogenicity and efficacy of Ervebo in children ~~aged~~ **less than** 1 ~~to 17~~ year~~s~~ **of age** have not ~~yet~~ been established (see sections 4.8 and 5.1). […]

Section 4.4

[…] Duration of protection

Vaccination with Ervebo may not result in protection in all vaccinees. Vaccine efficacy **in adults** has been established in the period ≥10 to ≤31 days after vaccination, however the duration of protection is not known (see section 5.1). […]

Transmission

[…] **In a Phase 1 study, vaccine viremia and** ~~V~~**v**iral shedding ~~was~~ **were** observed more frequently **(28/39)** in children and adolescents **6 to 17 years of age** ~~(28/39)~~ compared to adults. **In a subsequent Phase 2 study, 31.7% (19/60) of children and adolescents 1 to 17 years of age enrolled in a shedding sub-study shed vaccine virus in saliva following vaccination. Viral shedding was observed more frequently on Day 7 and declined thereafter, with no shedding detected at Day 56.**

[…] **Parents and caregivers of young vaccinees should observe careful hygiene especially when handling bodily waste and fluids for a minimum of 6 weeks after vaccination. Disposable nappies can be sealed in double plastic bags and disposed of in household waste. See section 5.3.**

Refer to the full PI for changes in sections 4.8, 5.1. and 5.3.

The Package Leaflet has been updated accordingly.

The MAH took the opportunity to correct the prescription status to "Medicinal product subject to medical prescription" in the Annex II of the PI. Therefore, the restriction, mistakenly included at the time of the initial MA, is deleted. CHMP agreed with this correction.

In addition, the list of local representatives in the package leaflet has been revised to amend contact details for the representative(s) of Germany and Italy.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to the currently approved package leaflet for Ervebo. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

EVD is an acute systemic febrile syndrome caused by EBOV with case fatality ranging from 25% to 90%. EBOV is highly contagious and spreads through human-to-human transmission directly or indirectly via blood or body fluids (e.g., urine, saliva, sweat, faeces, vomit, breast milk, and semen) of living or dead infected persons, or any soiled material.

While, historically, children have represented a small number of total cases of EVD, in recent outbreaks up to a quarter of cases have been in children. The largest outbreak, in West Africa, resulted in 28,616 cases, of whom approximately 18–20% were children, with a reported mortality rate of 42–63% in children <18 years and of 73–86% in children <5 years.

Younger children appear to have shorter mean incubation periods than adults and the disease also tends to have a shorter time course from symptom onset to hospitalisation and/or death compared to adults.

The pathogenesis of EVD is characterised by an intense inflammatory process, impaired haemostasis, and capillary leaks, with mortality resulting from septic shock and multi-organ system failure. Initial signs and symptoms are nonspecific (e.g., fever, headache, myalgia, fatigue) and may mimic other more common

conditions such as malaria. After a week, haemorrhagic manifestations can appear in more than half of the patients. EVD progresses with gastrointestinal symptoms, internal and external bleeding, and in some cases, rash, and neurologic involvement. The varying spectrum of EVD severity is increasingly described.

3.1.2. Available therapies and unmet medical need

Treatments

Treatment consists primarily of supportive therapy and is less than ideally effective, with case fatality rates remaining high even with intensive supportive care. The US FDA approved 2 monoclonal antibody therapies, REGN-EB3 (Inmazeb) in Oct-2020 and ansuvimab (Ebanga) in Dec-2020, for the treatment of infection caused by ZEBOV in adult and paediatric subjects. There are currently no specific approved medical interventions licensed to treat EVD in the EU.

Results from the PALM Phase 2/3 study showed a lower incidence in mortality at 28 days (primary endpoint). Nonetheless, 34% and 67% of patients with higher viral loads who received ansuvimab and REGN-EB3, respectively, in the study died and there remains an unmet medical need for more efficacious interventions.

Other vaccines

Ad26.ZEBOV and MVA-BN-Filo, also known as Zabdeno and Mvabea, respectively, is a 2-component vaccine regimen that was authorised under exceptional circumstances in the EU on 01-Jul-2020 and prequalified by the WHO for the prevention of disease caused by ZEBOV in individuals 1 year of age and older. Ad26.ZEBOV is administered first followed by MVA-BN-Filo approximately 8 weeks later as a booster. Clinical studies demonstrated that Ad26.ZEBOV/MVA-BN-Filo is safe and elicits strong neutralising and non-neutralising antibody responses; however, protective efficacy against EVD in humans has not been demonstrated.

Unmet medical need

EVD affects both adults and children. Younger children appear to have shorter mean incubation periods than adults, and the disease tends to have a shorter time course from symptom onset to hospitalisation and/or death compared to adults. Children < 5 years of age are especially vulnerable to EVD, with a reported mortality rate of 73-86% during the outbreak in West Africa from 2013 to 2016.

Only one prophylactic vaccine is available for preventing EVD in the paediatric population but the need for more than one dose and 2-month interval between doses make this vaccine regimen less suitable for an outbreak response in which immediate protection is necessary.

3.1.3. Main clinical study

The main clinical study is the V920-016 (PREVAC). The characteristics of this study are summarised in table 1 of section 2.3.1 (Clinical aspects introduction).

3.2. Favourable effects

V920 induces an increase in both neutralising and binding antibody titers against the vaccine virus and ZEBOV-GP, respectively, when compared to baseline, both in children and adults. Higher antibody titers than baseline values were observed up to 1-year post-vaccination.

The superiority of Day 28 and Month 12 GP-ELISA GMT in children 1 to 17 years of age vaccinated with 1 dose of V920 as compared with placebo was demonstrated, with a lower bound of the 2 sided 95% CI for

GMTR >1. Higher immune responses at Day 28 and Month 12 were also achieved for subgroup analyses by child age group, sex, and baseline serostatus.

Superior immune responses at 12 months were also achieved after 2 doses of V920 compared with placebo. However, humoral responses measured at Month 12 indicate that comparable responses were induced in participants randomised to 1 dose of V920 as compared to 2 doses of V920 at this later time-point.

The non-inferiority of the Day 28 GP-ELISA GMT in children (1-17 or 3-17 years of age) as compared to adults was demonstrated (lower bound of the 2-sided 95% CI greater than 0.67). Comparable immune responses at Day 28 were also achieved for subgroup analyses by sex, and baseline serostatus.

Seroresponse rates defined as a 2-fold increase from baseline and ≥200 EU/mL for GP-ELISA were high (>94%) at any time post-vaccination, and the majority (>85%) had a seroresponse defined as ≥4-fold increase from baseline. The proportions of participants with a GP-ELISA seroresponse defined as ≥4-fold increase from baseline were generally higher for children as compared to adults in the V920 groups at all time-points after vaccination. Most (>95%) children vaccinated with V920 had a PRNT seroresponse defined as ≥4-fold increase from baseline at any time post-vaccination.

3.3. Uncertainties and limitations about favourable effects

Clinical efficacy of V920 was not assessed in children and adolescents. Clinical efficacy of V920 was assessed in adults, in the ring vaccination study (Protocol 010). Vaccine efficacy was 100% (unadjusted 95% CI: 63.5% to 100%; 95% CI adjusted for multiplicity: 14.4% to 100%) (0 cases in the immediate arm; 10 cases in 4 rings in the delayed arm). Vaccine efficacy was only demonstrated in the period ≥10 to ≤31 days after vaccination. Uncertainties remain as to the actual level of protection, the duration of protection and the type of protection (pre- or post-exposure prophylaxis) given the methodological peculiarities of the ring vaccination design and the fact that the study was conducted during a declining Ebola epidemic.

It is currently not known if V920 protects against other EVD causing viruses.

The number of children and adolescents included in each age strata are limited, in particular children < 3 years. If considering the 1 dose V920 group only (as currently reflected in the SmPC), less than 50 children contributed to the Day 28 and Month 12 GP-ELISA and PRNT subgroup analyses. Immunogenicity data from ongoing trials are needed to confirm the level of immune responses induced by V920, in particular for the children <3 years of age. A better characterisation of the immune responses of V920 is also expected from the ongoing trials (kinetic, breath, booster response).

The immunogenicity data indicate a sustainable humoral immune response induced by V920 through one year, with antibody titers lower than at Day 28 but still higher than at pre-vaccination timepoint. The clinical relevance is unknown because of a lack of an ICP.

Long-term immunogenicity and the need/optimal timepoint for a booster dose are currently unknown.

No cell-mediated immunity data after vaccination in children are currently available.

There are no data on co-administration with other vaccines, hence co-administration is not recommended.

3.4. Unfavourable effects

In children and adolescents 1 to 17 years of age (in the V920 pooled group), the most common injection-site AE reported following vaccination with Ervebo were injection site pain (41.6%), injection-site pruritus

(4.1%), injection-site swelling (3.0%) and injection-site erythema (0.5%). The most common systemic AE (>7%) were pyrexia (62.2%), headache (45.7%), somnolence, reduced activity, fatigue (23.5%), decreased appetite (23.4%), abdominal pain (16.3%), myalgia (15.8%), chills (14.5%), dizziness (9.9%), vomiting (9.5%), and nausea (7.1%). In general, these reactions were reported within 7 days after vaccination and were mild to moderate in intensity.

The safety profile in the different age categories was in general comparable apart from pyrexia which was observed more frequently in the youngest age category (1 to 3 years of age). However, pyrexia was more frequent in the placebo arm in this population.

The proportions of children and adults who experienced an SAE were low and comparable for the pooled V920 and placebo groups from the first vaccination to the end of the base study.

Five children (3 in the 1-dose V920 group, 2 in the placebo group) and 4 adults (3 in the 1 dose V920 group, 1 in the placebo group) died during the study.

3.5. Uncertainties and limitations about unfavourable effects

The number of subjects in the age category from 1 to 3 years of age is rather limited. All safety data for the children vaccinated with V920 such as the long-term follow up of V920-016 (Protocol Version 5.0), studies V920-014 (CSR expected in 2024) and V920-015 (CSR expected in 2024), and the data set presented to SAGE by WHO, should be provided as soon as available.

With protocol version 3.0 (supportive data), there were only 10 children aged <3 years vaccinated with V920 (8 in the 1 dose group, and 2 in the 2-dose group).

Viral shedding/secondary transmission to close contacts, particularly immunocompromised hosts, is an important potential risk in the RMP.

3.6. Effects Table

Table 46. Effects Table for Ervebo (paediatric population)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Immunogenicity	GP ELISA – Day 28, children V920 vs children Placebo	N of subjects	499	173		CLINICAL STUDY P016V01V920
		GMT (95% CI)	1,748.8 (1,585.6, 1,928.7)	96.4 (81.6, 113.8)	**SoE:** GMTR (95% CI), p value: 18.15 (14.96, 22.01), <0.001, superiority **Unc:** No ICP, limited number of children <3 yoa	
	GP ELISA – Day 28, children V920 vs adults V920	N of subjects	499	519		
		GMT (95% CI)	1,748.8 [1,585.6, 1,928.7]	1,234.4 [1,132.5, 1,345.4]	**SoE:** GMTR (95% CI), p value: 1.42 (1.24, 1.62), <0.001, non-inferiority **Unc:** No ICP, limited number of children <3 yoa	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	PRNT – Day 28, children V920 and Placebo	N of subjects	266	130		
		PRNT GMT [95% CI]	281.9 [255.3, 311.0]	17.8 [15.5, 20.5]	**SoE:** GMT higher than at baseline and placebo **Unc:** No ICP, limited number of children <3 yoa	
Unfavourable Effects						
Injection site reactions		%	43.6	13.1		CLINICAL STUDY P016V01V920
Abdominal pain		%	16.3	12.1		
Arhralgia		%	6.9	3.6		
Chills		%	14.5	11.3		
Crying		%	6.4	2.3		
Decreased appetite		%	23.4	13.9		
Diarrhoea		%	5.8	6.2		
Dizziness		%	9.9	5.9		
Headache		%	45.7	31.4		
Hyperhidrosis		%	2.6	1.8		
Irritability		%	2.1	0.3		
Joint swelling		%	0.5	0.5		
Mouth ulceration		%	2.5	0.5		
Myalgia		%	15.8	5.2		
Nausea		%	7.1	4.6		
Pyrexia		%	62.2	38.7		
Screaming		%	1.8	0.5		
Skin lesion		%	4.9	8.2		
Somnolence		%	23.5	12.6		
Vomiting		%	9.5	7.2		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Although there are no established immunological correlates of protection, the demonstration of (at least) comparable humoral immune responses (both GP-ELISA and PRNT) in children versus adults is deemed appropriate to reasonably assume a benefit of V920 in protecting children. The actual level of protection is unknown as well as the duration of protection.

The unfavourable effects that were identified in the paediatric population were in accordance with what was seen in adults.

The safety profile in the different age categories is in general comparable apart from pyrexia which was observed more frequently in the youngest age category (1 to 3 years of age). However, pyrexia was also more frequent in the placebo arm in this population.

The number of subjects <3 years of age was limited but deemed acceptable to support the requested extension of indication given that children <5 years of age are especially vulnerable to EVD, with a reported mortality rate of 73-86% during the outbreak in West Africa from 2013 to 2016. In addition, the use of V920 within the European context is considered to be very specific, i.e., mainly Health Care Workers.

Safety and immunogenicity data from the 5-years ongoing follow-up of V920-016 and from ongoing trials (V920-014 and V920-015) are requested to be submitted as available. Effectiveness and safety data for the paediatric population of the V920-EAP5 study (included in the RMP) are also to be provided.

3.7.2. Balance of benefits and risks

The immunogenicity of 1 dose of V920 was shown to be (at least) comparable in children 1 to 17 years of age and in adults, which shows a benefit of V920 in protecting children.

The overall safety profile in the paediatric population (from 1 to 17 years of age) is in accordance with the safety data in adults after 1 dose of V920. No new safety signal was identified.

The number of subjects in the age category from 1 to 3 years of age is rather limited but deemed acceptable to support the requested extension of indication. The safety and immunogenicity profiles will be further confirmed with the results of ongoing studies.

3.8. Conclusions

The overall benefit/risk balance of Ervebo in the sought after indication is positive.

The following measures are considered necessary to address issues related to immunogenicity and safety:

Recommendation (REC):

- **REC 1:** Results of the long-term follow up of PREVAC/V920-016 (Protocol Version 5.0) should be submitted as soon as available.
- **REC 2:** Results of V920-014 (CSR expected in 2024) should be submitted as soon as available.
- **REC 3:** Results of V920-015 (CSR expected in 2024) should be submitted as soon as available.
- **REC 4:** Analysis of safety data set presented to SAGE by WHO (March 2021) should be submitted as soon as available.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the paediatric population from 1 year to less than 18 years of age based on final results from study V920-016 (PREVAC); this is a phase 2, randomised, double-blind, placebo-controlled study of 2 leading Ebola vaccine candidates (Ad26.ZEBOV/MVA-BN-Filo and V920) and 3 vaccine strategies (Ad26.ZEBOV/MVABN-Filo, 1-dose V920, and 2 dose V920) to evaluate immunogenicity and safety in healthy children and adolescents from 1 to 17 years of age and adults 18 years of age and

older. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.3 of the SmPC are updated.

The Package Leaflet is updated in accordance.

Version 2.0 of the RMP has also been approved.

In addition, the MAH took the opportunity to update the Annex II and the list of local representatives in the Package Leaflet.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

This recommendation is subject to the following amended condition:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.