European Union Risk Management Plan
VAC52150 (Ad26.ZEBOV-GP [ZABDENO], MVA-BN-Filo [MVA-mBN226B, MVABEA])

Data lock point for current RMP	21 Dec 2023	Version number	4.1

CHMP Opinion Date: 27 February 2025

QPPV Sign-off Date: 25 February 2025
RMP Version Number: 4.1
Supersedes Version: 3.2
EDMS Number: EDMS-RIM-1532151, 2.0

QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	4.1
Rationale for submitting an updated RMP (if applicable)	Type II variation to remove the missing information 'Use during pregnancy' based on completion of the category 3 additional pharmacovigilance activity VAC52150EBL3010 (EBL3010).
Summary of significant changes in this RMP	Safety concerns: • Removal of 'Use during pregnancy' as a missing information. Pharmacovigilance Plan: • Removal of 'cumulative reviews of individual case safety reports following exposure to Ad26.ZEBOV and MVA-BN-Filo during pregnancy' as other forms of routine pharmacovigilance activities due to removal of the missing information 'Use during pregnancy'. • Removal of Trial EBL3010 as a category 3 pharmacovigilance activity due to completion of the study. Postauthorization Efficacy Plan: • Inclusion of the study number and protocol for the postauthorization efficacy study which is a specific obligation in the context of a marketing authorization under exceptional circumstances (VAC52150EBL4006).

Other RMP Versions Under Evaluation:

RMP Version Number	Submitted on	Procedure Number
Not applicable		

Details of the Currently Approved RMP:

Version number of last agreed RMP	3.2
Approved within procedure	PSUSA/00010857/202309
Date of approval (Competent authority opinion date)	25 April 2024

TABLE OF CONTENTS

TABLE OF CONTENTS **4**

PART I: PRODUCT(S) OVERVIEW **6**

PART II: SAFETY SPECIFICATION **8**

MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S) **8**

MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION **15**

MODULE SIII: CLINICAL TRIAL EXPOSURE **19**
SIII.1. Brief Overview of Development 19
SIII.2. Clinical Trial Exposure 22

MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS **28**
SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program 28
SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs 31
SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s) 32

MODULE SV: POSTAUTHORIZATION EXPERIENCE **41**
SV.1. Postauthorization Exposure 41
SV.1.1. Method used to Calculate Exposure 41
SV.1.2. Exposure 41

MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION **42**

MODULE SVII: IDENTIFIED AND POTENTIAL RISKS **43**
SVII.1. Identification of Safety Concerns in the Initial RMP Submission 43
SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP 43
SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP 49
SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP 49
SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information 50
SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks 50
SVII.3.2. Presentation of the Missing Information 52

MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS **53**

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES) **54**
III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection 54
III.2. Additional Pharmacovigilance Activities 54
III.3. Summary Table of Additional Pharmacovigilance Activities 54

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES **55**

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES) **57**
V.1. Routine Risk Minimization Measures 57
V.2. Additional Risk Minimization Measures 57
V.2.1. Removal of Additional Risk Minimization Activities 57
V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities 58

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN **59**
I. The Vaccine and What it is Used For 59
II. Risks Associated with the Vaccine and Activities to Minimize or Further Characterize the Risks 60

II.A. List of Important Risks and Missing Information 60
II.B. Summary of Important Risks 61
II.C. Postauthorization Development Plan 61
II.C.1. Studies Which are Conditions of the Marketing Authorization 61
II.C.2. Other Studies in Postauthorization Development Plan 61

PART VII: ANNEXES 62
Annex 4: Specific Adverse Drug Reaction Follow-up Forms 63
Annex 6: Details of Proposed Additional Risk Minimization Activities (if Applicable) 64

PART I: PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	Ebola vaccine (Ad26.ZEBOV-GP [recombinant]), further referred to as Ad26.ZEBOV Ebola vaccine (MVA-BN-Filo [recombinant]), further referred to as MVA-BN-Filo
Pharmacotherapeutic group(s) (ATC Code)	Vaccine, other viral vaccines (ATC code: J07BX02)
Marketing Authorization Holder (MAH)	Janssen-Cilag International N.V.
Vaccines to which the RMP refers	2
Invented name(s) in the European Economic Area (EEA)	ZABDENO (for Ad26.ZEBOV) MVABEA (for MVA-BN-Filo)
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class:** Ad26.ZEBOV is a recombinant, replication-incompetent vectored monovalent vaccine. MVA-BN-Filo is a recombinant, non-replicating in human cells vectored multivalent vaccine.
	Summary of mode of action: Ad26.ZEBOV is a monovalent vaccine composed of a single, recombinant, replication-incompetent human adenovirus type 26 (Ad26) vectored vaccine that encodes the *Zaire ebolavirus* (EBOV) Mayinga variant glycoprotein (GP). MVA-BN-Filo is a recombinant, non-replicating in human cells, Modified Vaccinia Ankara – Bavarian Nordic (MVA-BN) vectored multivalent Filovirus vaccine that encodes the EBOV Mayinga variant GP, the *Sudan ebolavirus* (SUDV) Gulu variant GP, the *Marburg marburgvirus* (MARV) Musoke variant GP, and the *Taï Forest ebolavirus* (TAFV) nucleoprotein. The EBOV GP encoded by Ad26.ZEBOV has 100% homology to the one encoded by MVA-BN-Filo. Following administration, the EBOV GP is expressed locally and stimulates an immune response.
	Important information about its composition: Ad26.ZEBOV is produced in PER.C6 cells and by recombinant DNA technology. MVA-BN-Filo is produced in chicken embryo fibroblast cells and by recombinant DNA technology. Ad26.ZEBOV and MVA-BN-Filo contain genetically modified organisms. MVA-BN-Filo contains trace residues of chicken or egg protein and gentamicin.

Reference to the Product Information	Module 1.3.1, Summary of Product Characteristics, Labeling and Package Leaflet	
Indication(s) in the EEA	**Current:** Ad26.ZEBOV and MVA-BN-Filo, as part of the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen, are indicated for active immunization for prevention of disease caused by Ebola virus (*Zaire ebolavirus* species) in individuals ≥1 year of age.	
	Proposed: Not applicable	
Dosage in the EEA	**Current:** Ad26.ZEBOV and MVA-BN-Filo are used in the prophylactic 2-dose heterologous Ebola vaccine regimen. A dose (0.5 mL) of Ad26.ZEBOV vaccine should be administered as the first vaccination. A dose (0.5 mL) of MVA-BN-Filo vaccine should be administered as the second vaccination approximately 8 weeks after the first vaccination with Ad26.ZEBOV. Individuals who have previously completed the 2-dose primary vaccination regimen can receive a booster dose of Ad26.ZEBOV. As a precautionary measure, an Ad26.ZEBOV booster vaccination is recommended in individuals who are at imminent risk of exposure to Ebola virus and have completed the 2-dose primary vaccination regimen more than 4 months ago. Ad26.ZEBOV and MVA-BN-Filo should be administered by the intramuscular route. The preferred site is the deltoid muscle of the upper arm. In younger children, either the deltoid region of the arm or anterolateral aspect of the thigh are acceptable sites for intramuscular injection.	
	Proposed: Not applicable	
Pharmaceutical form(s) and strengths	**Current:** Ad26.ZEBOV is presented as a colorless to slightly yellow, clear to very opalescent suspension for intramuscular injection. A single dose of Ad26.ZEBOV contains not less than 8.75 $\log_{10}$ infectious units (Inf.U) in 0.5 mL. MVA-BN-Filo is presented as a light yellow, clear to milky suspension for intramuscular injection. A single dose of MVA-BN-Filo contains not less than $0.7x10^8$ Inf.U in 0.5 mL.	
	Proposed: Not applicable	
Is/will the product be subject to additional monitoring in the EU?	☑ **Yes**	☐ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

Indication: Ebola Virus Disease

The outbreak of a particularly virulent form of hemorrhagic fever in 1976 in Sudan and Zaïre (now Democratic Republic of the Congo [DRC]) led to the discovery of the Ebola virus as the causative agent (CDC 2023). Since that time, 6 species of Ebola virus have been identified: EBOV, SUDV, *Bundibugyo ebolavirus* (BDBV), TAFV, *Reston ebolavirus* (RESTV), and *Bombali ebolavirus* (BOMV) that was discovered in 2018 (Goldstein 2018, Kuhn 2019). While multiple severe epidemics were associated with EBOV and SUDV, there have been 2 limited outbreaks with BDBV and a single nonfatal case associated with TAFV to date; RESTV has not caused disease in people and it is not known at this stage if BOMV, recently identified in bats, can be pathogenic (CDC 2023). Ebola viruses belong to the Filoviridae family together with the closely related MARV which, as EBOV and SUDV, can cause fatal hemorrhagic fever (Nyakarahuka 2016).

Incidence and Prevalence (Outbreaks):

In the decades that followed the discovery of Ebola virus and until end 2013, sporadic outbreaks of Ebola virus disease (EVD) occurred in equatorial Africa, with, in total, approximately 2,300 cases and an average fatality rate of 78% (CDC 2018). The EBOV outbreak that started in December 2013 and affected Guinea, Liberia, and Sierra Leone showed a fast escalation in the number of EVD cases and fatalities. The epidemic was declared a Public Health Emergency of International Concern (PHEIC) in August 2014 (WHO 2014c). A total of 28,646 cases and 11,323 deaths were reported over the outbreak duration (2014-2016) (Lo 2017). However, because of underreporting, the true burden might have been higher (Malvy 2019). It was the first EVD outbreak to reach other continents beyond Africa, with cases in Europe (Spain, Italy, and the United Kingdom) and North America (United States). From 2013 to 2014, Spain, Italy, and the United Kingdom each reported 1 case of Ebola and the United States reported 4 cases of Ebola.

The second largest outbreak after the 2014-2016 West-African outbreak was reported in the DRC from August 2018 to June 2020. On 25 June 2020, the World Health Organization (WHO) declared the outbreak over with a total of 3,470 cases (probable and confirmed) and 2,287 deaths with an overall case fatality rate (CFR) of 66% (WHO 2020). This Ebola outbreak was declared a PHEIC on 17 July 2019 (WHO 2019c). On 13 June 2019, the Ugandan Ministry of Health confirmed 3 cases of EVD in the Kasese District in a family that crossed the border from the DRC. This cross-border spread is of concern and highlights the continuing vulnerability of the region (Government of Uganda 2019). The confirmed cases in Uganda represent the first cases of EBOV in the country, and the first cases of EVD in Uganda since 2013 (CDC 2020).

Three EVD outbreaks have since been declared in the DRC. The most recent one started in October 2021 and was the 13th EVD outbreak in the DRC. The outbreak was declared officially over on 16 December 2021, 42 days after the last confirmed case of EVD was released from the Ebola treatment unit after testing negative twice for Ebola. Sequencing genomic data showed that the outbreak could be a flare-up of the EVD outbreak of 2018-2020 in the DRC, and was not the result of a new zoonosis from an animal reservoir (CDC 2022).

In Guinea, the first Ebola outbreak since the large 2014-2016 West-African outbreak was recorded from 14 February to 19 June 2021. A total of 23 cases (16 confirmed, 7 probable) were identified in 4 sub-prefectures of N'Zérékoré Prefecture. Of these confirmed and probable cases, 11 were non-fatal and 12 were fatal. On 19 June 2021, the Ministry of Health of Guinea declared the end of the Ebola outbreak that affected N'Zérékoré Prefecture (CDC 2021b).

In 2022, sporadic outbreaks of Ebola occurred in various regions, including the North Kivu Province and the Mbandaka health zone of the Equateur Province in the DRC, and Uganda. The sequencing results of the North Kivu outbreak, conducted by the INRB lab in Goma, revealed a connection between this case and the 2018-2020 EVD outbreak in the same region. This suggests a relapse of EVD or infection by a survivor experiencing a relapse or persistent EVD infection.

In the Mbandaka health zone of Equateur Province, the outbreak began with a confirmed case resulting from a new spillover event from an animal to a person, unrelated to previous outbreaks. Subsequently, 4 cases were identified, all of which were epidemiologically linked or had contact with an individual infected with EVD. The outbreak concluded on 4 July 2022.

Demographics of the Population in the Indication - Age, Sex, Racial and/or Ethnic Origin, and Risk Factors for the Disease

Age:

The disease affects all age groups in the population (Olupot-Olupot 2015).

During the 2014-2016 West-African outbreak in Guinea, the CFR of EVD was significantly higher in the ≥60 years age group (80.6%) (P<0.001) compared with the 20-59 years age group. In a multivariable analysis, there was a significant association between increasing age and risk of death due to EVD in the ≥60 years age group (odds ratio [95% confidence interval (CI)]: 1.05 [1.003-1.098]; P=0.036). However, no clinical symptom was found to be predictive of the poor outcome in EVD among the ≥60 years age group (Cherif 2018).

During the 2018-2020 DRC outbreak, there were 27 cases among infants <1 year of age, with 70% (19) of these being boys, and 21 fatalities (age-specific case fatality of 78%), as of 4 December 2018. There were also 9 cases in infants aged <1 month (WHO 2018a). The highest number of cases was reported in the 15-49 years age group, with 60% (355/589) of the cases reported as of 26 December 2018 in Northern Kivu and Ituri (WHO 2018b). As of 7 July 2019, children <5 years of age accounted for 40% of the 750 cases reported among children; this represents 31% of the total cases, compared with about 20% in previous outbreaks (Mercado 2019). As reported in the WHO Situation Report on the DRC outbreak that started in August 2018, children aged <18 years accounted for 29% (1,002/3,470) of overall cases as of 21 June 2020 (WHO 2020).

Sex:

During the 2014-2016 West-African outbreak, more cases were recorded among women than men. In a study conducted by the WHO Ebola response team during the 2014 outbreak to assess sex differences among 20,035 cases reported in the 3 most affected countries (Guinea, Liberia, and

Sierra Leone), women and men had a similar average risk of contracting the virus. The frequency of exposure was higher among women than men (34.3%, 95% CI: 33.4-35.2 versus 30.7%, 95% CI: 29.8-31.7; P < 0.001) (Nkangu 2017).

In the 9 Ebola outbreaks in the DRC that occurred before August 2018, infection rates were relatively equal in men and women. In the DRC outbreak that started in August 2018, women accounted for 57% (1,970/3,470) of overall cases where sex was reported, as of 21 June 2020 (WHO 2020). The disparity in this outbreak may be due to gender roles in the DRC North Kivu province. In this province, women are often the heads of their households. They are responsible for caring for the sick, taking them to the hospital or preparing bodies for a burial, all of which can expose them to Ebola (Bean 2019).

The incidence of EVD in pregnant women remains uncertain due to the low number of women affected in previous outbreaks and limitations in data collection (Black 2015, Haddad 2018).

Racial and/or Ethnic Origin:

Ebola hemorrhagic fever outbreaks have mostly been reported in African countries (such as DRC, Gabon, Sudan, Ivory Coast, Guinea, Liberia, Sierra Leone, and Uganda) (CDC 2021a).

Risk Factors for the Disease:

Ebola virus disease can spread through human-to-human transmission via direct contact with body fluids (like blood, feces, vomit), through broken skin or mucous membranes of a person infected with Ebola or who has died from Ebola, or via contact with objects that have been contaminated with body fluids from such a person. Ebola viruses have the ability to remain viable on dry surfaces such as doorknobs and countertops for several hours. In body fluids, particularly blood, Ebola viruses can survive for several days at room temperature (CDC 2023). Nearly all pregnant women with EVD had adverse pregnancy outcomes. Among survivors, Ebola virus RNA was detected by reverse transcription polymerase chain reaction in amniotic fluid up to 32 days after maternal clearance of Ebola virus from the blood and in breastmilk 26 days after symptom onset (Foeller 2020).

During Ebola hemorrhagic fever outbreaks, healthcare workers and family members and friends associated with an infected person are at the highest risk of getting the disease. As reported on 21 June 2020 in the WHO Situation Report of the DRC outbreak that started in August 2018, 5% (171/3,470) of overall cases were healthcare workers (WHO 2020). In a recent Ebola outbreak in Guinea, of 23 confirmed cases, 5 were healthcare workers and 1 was a traditional health practitioner (WHO 2021a). Caring for infected persons who are near-death or disposing of bodies of individuals that have recently died of Ebola infection poses the highest risk, because in these situations, the Ebola virus is highly concentrated in any blood or bodily secretions. People remain infectious as long as their blood contains the virus (WHO 2019a). A recent analysis suggests that Ebola survivors can experience relapses and potentially trigger outbreaks up to 5 years after initial infection, as seen in the 2021 outbreak in Guinea. Long-term follow-up of former patients is vital to prevent potentially devastating flare-ups. The virus can lie dormant in survivors' tissues, causing negative test results despite its presence (Keita 2021).

Travelling to areas with reported Ebola infections poses a risk in developing Ebola hemorrhagic fever. Ebola virus disease can spread easily due to the high rates of international travel, and secondary infection from patients that travelled from African countries. Such cases have been reported in Spain, Italy, the United Kingdom, and the United States. Imported cases in Europe occurred in the following scenarios: in Spain, a healthcare worker involved in the care of patients repatriated from West Africa (Sierra Leone and Liberia) (WHO 2014a); in Italy, a returning healthcare worker volunteered at an Ebola treatment center in Sierra Leone (WHO 2015a); and in the United Kingdom, a case was imported into Scotland in December 2014, the patient was a healthcare worker who had been working in an Ebola treatment center in Sierra Leone (WHO 2014b). Unfamiliarity with EVD outside of the endemic area has led to delayed diagnosis of imported cases (Malvy 2019).

Researchers who study Ebola hemorrhagic fever viruses are also at risk of developing the disease if a laboratory accident occurs. In addition, association with wild animals (mainly primates in the area with reported Ebola infections) is a potential health risk factor according to the Centers for Disease Control and Prevention (CDC). This includes eating or handling “bush meat”, which is the meat of wild animals, including hoofed animals, primates, bats, and rodents. Evidence for any airborne transmission of the virus is lacking (Davis 2019).

Main Existing Treatment and Prevention Options:

In the European Union (EU), there is no approved treatment for EVD. Standard treatment is mainly supportive and consists of provision of fluids and electrolytes, maintaining blood pressure and oxygen status, and managing fever and pain (CDC 2017a). Supportive care in the hospital has been shown to increase the chances of survival (Lamontagne 2019).

The European Medicines Agency (EMA) has identified 4 treatments that could potentially be made available to patients, if required. These include 3 treatments based on monoclonal antibodies (mAbs) all targeting the EBOV GP (ZMapp, mAb114, and REGN-EB3) and an inhibitor of viral RNA synthesis (remdesivir). ZMapp is composed of 3 chimeric mAbs (Qiu 2014), mAb114 is based on an isolate from a survivor of the 1995 outbreak of EVD in Kikwit, the DRC (Corti 2016), REGN-EB3 is a cocktail of 3 humanized mAbs (Sivapalasingam 2018), and remdesivir is a small-molecule nucleotide prodrug (Agostini 2018).
In the US, there are currently 2 treatments approved by the Food and Drug Administration (FDA) to treat EVD caused by the Ebola virus, species Zaire ebolavirus, in adults and children. The first drug approved in October 2020, Inmazeb, is a combination of 3 monoclonal antibodies. The second drug, Ebanga, is a single monoclonal antibody and was approved in December 2020. Both treatments are not approved in the EU.

To date, 5 Ebola virus vaccines have been submitted for marketing approval or have been approved, of which 4 recombinant viral-vectored vaccines that encode for the EBOV GP (ie, rVSV-ZEBOV-GP, Ad5.EBOV, rVSV-ZEBOV followed by rAd5-EBOV, and Ad26.ZEBOV followed by MVA-BN-Filo), and one conjugate vaccine (ie, EPIVAC).

Two vaccine regimens (Ad5.EBOV single-dose; and rVSV-ZEBOV followed by rAd5-EBOV), developed from the circulating strain of the 2014-2016 West-African outbreak, are approved for

human use in China (approved in 2017 for emergency use in case of an outbreak) and Russia, respectively (Zhu 2017, Cansino 2019, Dolzhikova 2017). The conjugate EPIVAC vaccine (2-dose regimen) is based on 2 chemically synthesized peptide antigens of Ebola virus proteins conjugated to a protein carrier (undefined), and is licensed for human use in Russia since 2016. An Ebola-specific antibody response was generated in 95% (170/179) of evaluable participants (Tomori 2021).

The rVSV-ZEBOV-GP vaccine demonstrated 100% efficacy in a reactive ring vaccination study during the 2014-2016 West-African outbreak (Henao-Restrepo 2017). This vaccine was used for reactive ring vaccination in the 2018-2020 outbreak in the DRC through the Expanded Access Framework of the WHO (SAGE 2019, WHO 2019e). On 11 November 2019, EMA granted conditional marketing authorization for Ervebo (rVSV-ZEBOV-GP), which was switched to a full marketing authorization on 14 January 2021 for active immunization of individuals aged 18 years and older at risk of infection with the Ebola virus (Ervebo 2021). In December 2020, the vaccine was prequalified by the WHO for use in individuals 18 years of age and older (except for pregnant and breastfeeding women) for protection against EVD caused by EBOV (WHO 2021b).

Despite progress made in outbreak control methods and the implementation of ring vaccination with the rVSV-ZEBOV-GP vaccine, the frequent recurrence of outbreaks in the DRC highlights that a reactive vaccination response is not always capable on its own to interrupt transmission and quickly curtail an outbreak. The increased frequency and magnitude of outbreaks since 2013 indicate that Ebola is becoming a prominent part of the epidemiological landscape and possibly a permanent public health threat in Sub-Saharan Africa.

The main measures applied to avoid transmission during historical outbreaks have been isolation of patients and of their contacts and the use of safe burial procedures. Despite these efforts, mortality remains high and epidemics lead to severe social disruption through economic shutdown, weakening of sociopolitical systems, and psychological distress (Omoleke 2016, Van Bortel 2016). Consequences are devastating and can persist for decades (Menéndez 2015).

In addition to standard control measures, prophylactic vaccination campaigns may be more successful in preventing future outbreaks in areas suffering from recurring Ebola outbreaks.

A conditional approval under an exceptional emergency situation was granted for the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen by the Rwanda Food and Drugs Authority (Rwanda FDA) on 27 September 2019. This approval was subsequently extended for an additional year. Consequently, the Unprecedented Movement to drive a Unified Rwandan Initiative for National ZEBOVAC Immunization (UMURINZI) Ebola Vaccination Campaign was launched (VAC52150EBL4002). This was a large-scale population-based program to deliver the Ebola vaccine regimen VAC52150 (Ad26.ZEBOV and MVA-BN-Filo) to approximately 200,000 adults, non-pregnant women, adolescents, and children aged 2 years or older living in the vicinity of an Ebola outbreak. The vaccinations with the Ad26.ZEBOV, MVA-BN-Filo Ebola vaccine regimen in Rwanda started on 8 December 2019 and were completed on 14 September 2021. Full Marketing Authorization in Rwanda was granted on 13 March 2023.

In July 2020, EMA granted marketing authorization for the 2-dose heterologous Ad26.ZEBOV, MVA-BN-Filo Ebola vaccine regimen for individuals 1 year and older under the trade names ZABDENO and MVABEA, respectively, although the products have not yet been administered in EU markets. Because this vaccine is delivered in 2 doses (Ad26.ZEBOV first and MVA-BN-Filo approximately 8 weeks later as a second dose), this prophylactic 2-dose regimen is not suitable for an outbreak response ring vaccination where immediate protection is necessary (WHO 2021b). However, the vaccine regimen is recommended both during outbreaks for individuals at some risk of Ebola exposure (ie, in neighboring areas and countries where the outbreak may spread) and preventively, before outbreaks, for national and international first responders (WHO 2021c). On 3 May 2021, a "Temporary Authorization for Use" was granted by the health authority of the DRC (la Direction de la Pharmacie et du Médicament) to deploy the Ad26.ZEBOV, MVA-BN-Filo vaccine in the DRC. Both vaccines received WHO prequalification in April 2021 and have been approved in Ghana (17 March 2022), Cote d'Ivoire (14 June 2022), Gabon (17 February 2023), Rwanda (13 March 2023), Sierra Leone (14 March 2023), Uganda (29 March 2023), and Nigeria (31 May 2023).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Ebola virus disease is a zoonosis, with probable reservoir in bats, that is transmitted by direct contact with body fluids or tissues of an infected individual during epidemics. The typical disease course is rapid and unspecific symptoms such as fever, malaise, chills, and myalgia appear abruptly, on average 6 to 10 days after infection. Signs of hemorrhage, including petechiae and rashes, appear at the peak of infection usually by Day 5 to 7 of the illness. As infection disseminates, multiorgan failure is incurred, leading to severe bleeding and shock. In patients with fatal outcome, death occurs within 6 to 16 days of disease onset (Feldmann 2011). In most cases, people who have completely recovered from EVD do not go through a comeback of the illness (CDC 2017b). EVD has been noted to persist in immune-privileged sites including the aqueous humor and cerebrospinal fluid, leading to severe uveitis and meningoencephalitis, respectively, during EVD convalescence. Long-term EBOV RNA detection in semen, breast milk, and placenta with rare transmission events was reported (Shantha 2018).

EBOV is historically associated with the highest mortality rates (88% in the 1976 outbreak) and is a public health concern together with SUDV and MARV in equatorial Africa (Feldmann 2011).

In past outbreaks, the CFR ranged from 25% to 90%, with an average CFR of 50% (WHO 2019a). The EBOV species has the highest mortality rate (60%-90%) followed by the SUDV species (40%-60%).

During the 2014-2016 West-African outbreak, the CFR for adults (age ≥45 years) was 83.8%. The estimated CFR for confirmed and probable cases of EVD in children varies with age. The rates for children ranged from 55.8% (for 10- to 15-year-olds) to 91.2% (for children <1 year of age) (Aswani 2016). The CFR was high for EBOV-infected children younger than 5 years (Glynn 2015, WHO 2015b, Fitzgerald 2016). During the DRC outbreak that started in August 2018, children accounted for approximately one third of the Ebola cases (Unicef 2018). As of 28 May 2019, the

overall CFR of EVD in children under the age of 5 was 77%, which is notably higher than in older children, confirming figures of the 2014-2016 West-African outbreak (WHO 2019b).

In the 1976 outbreak in the DRC, the mortality rate was 56% among women and 44% among men. Similarly, of the 315 cases reported in a 1995 nosocomial outbreak, 53% were in women, and 47% were in men (Nkangu 2017). The pregnancy-specific mortality rate has been difficult to discern based on published findings but is suspected to be between 74% and 93%. The fetal loss rate is nearly 100% for pregnant women with EVD (Olgun 2018, Sayres 2020). The maternal CFR among pregnant women with EVD during the 2018-2020 DRC outbreak was high: 73 of the 82 infected women who were pregnant died, a case (maternal) mortality rate of 89%. The rate of spontaneous abortions was 23% (19/82). During this outbreak, all 10 liveborn infants that were delivered to infected mothers subsequently died within 19 days of life from Ebola virus infection (Schwartz 2020). As of 21 June 2020, the overall CFR during the 2018-2020 DRC outbreak was 66% (WHO 2020).

Important Comorbidities:

Important comorbidities for EVD include human immunodeficiency virus (HIV) and other prevalent tropical diseases in the zone where the outbreak happens such as malaria, yellow fever, and helminthiasis.

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

The nonclinical safety profile of Ad26.ZEBOV and MVA-BN-Filo was assessed in 2 pivotal good laboratory practice (GLP) toxicology studies in New Zealand White (NZW) rabbits, ie, a general (repeat-dose) toxicity study including local tolerance, and a combined embryo-fetal and pre- and postnatal development (EF-PPND) study. In addition, the nonclinical safety profile of either MVA-BN-Filo alone or regimens of MVA-BN-Filo and a multivalent Ad26.Filo vaccine (ie, a trivalent mixture of Ad26.ZEBOV with 2 other Ad26 vectors encoding the GPs of the SUDV Gulu variant [Ad26.SUDV] and the MARV Angola variant [Ad26.MARVA] in a 1:1:1 ratio) was evaluated in separate supportive GLP general (repeat-dose) toxicity studies in NZW rabbits. Biodistribution studies were conducted in NZW rabbits to assess the distribution, persistence, and clearance of the Ad26 and MVA-BN viral vector platforms. The testing was consistent with the WHO Guidelines on Nonclinical Evaluation of Vaccines (WHO 2005), the EMA Guideline on quality, non-clinical and clinical aspects of live recombinant viral-vectored vaccines (EMA 2010), and the United States Food and Drug Administration (FDA) Guidance for Industry - Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications (FDA 2006).

In line with the applicable guidelines, safety pharmacology, genotoxicity, and carcinogenicity studies have not been conducted.

The nonclinical safety (and biodistribution) studies were conducted using the intramuscular route, which is also the intended route for use of Ad26.ZEBOV and MVA-BN-Filo in humans. The rabbit was considered a relevant toxicological species because both Ad26.ZEBOV and MVA-BN-Filo were shown to elicit specific antibody responses against the GP antigen of the Ebola virus in these animals. The vaccine dosages applied were at least equal to the recommended human dose level, hence full human dose levels were tested. Various vaccine regimens were tested in the pivotal and supportive nonclinical safety studies, including the heterologous 2-dose vaccine regimen that is approved for human use (ie, a first dose of Ad26.ZEBOV, followed by a second dose of MVA-BN-Filo). The booster vaccination with Ad26.ZEBOV that may be administered to individuals who have previously completed the 2-dose primary vaccination regimen was covered through the supportive GLP toxicology study which tested a sequential Ad26.Filo, MVA-BN-Filo, Ad26.Filo regimen.

The nonclinical biodistribution studies showed a limited distribution profile of the Ad26 and MVA-BN vectors, and clearance of the vectors was observed. There were no adverse vaccine-related effects noted in the available pivotal and supportive nonclinical safety studies. All vaccine-related effects were considered to reflect a normal, physiological response associated with vaccination.

Following reports of very rare cases of thrombosis in combination with thrombocytopenia after vaccination with Ad26.COV2.S (an Ad26-based COVID-19 vaccine), nonclinical studies were performed to gain insight into the potential mechanisms of (vaccine-induced) TTS.

Two studies relevant to the Ad26 vector platform are described in this Section. Firstly, it was investigated in rabbits if potential accidental intravenous injection of Ad26.COV2.S could be involved in TTS. Although based on a limited number of animals, the data indicate that an accidental intravenous injection of Ad26.COV2.S may not represent an increased risk of TTS. Secondly, it became apparent that the presence of anti-platelet factor 4 (PF4) antibodies appears to be a central mechanistic aspect of TTS pathogenesis (Buoninfante 2022, Marietta 2022, Toh 2022). Vaccine-induced TTS has been found to resemble heparin-induced thrombocytopenia (HIT), which is thought to be caused by antibodies that are induced by complexes of heparin and PF4 and that can induce Fc-receptor-mediated activation of platelets and hypercoagulation (Greinacher 2021b, Schultz 2021). However, the induction of anti-PF4 antibodies in TTS is independent of heparin use (Li 2021). It has been hypothesized that Ad26.COV2.S or another component in the vaccine can mimic the role of heparin in binding to PF4 and as such trigger the induction of anti-PF4 antibodies (Baker 2021, Greinacher 2021a). The potential direct interaction between PF4 and Ad26.COV2.S has been assessed using 3 different biophysical techniques: dynamic light scattering (DLS), biolayer interferometry (BLI), and surface plasmon resonance (SPR). In DLS and BLI experiments, no direct interactions between PF4 and Ad26.COV2.S nor the Ad26 capsid hexon (tested using BLI) were observed. SPR data demonstrated that the induced binding of PF4 to Ad26.COV2.S as published by Baker et al. (Baker 2021) is likely an experimental artefact. These findings are in line with findings of Michalik et al. (Michalik 2022) using DLS, showing no complex formation of PF4 with Ad26.COV2.S. Therefore, it is unlikely that direct binding of Ad26 vector particles to PF4 is driving the etiology of TTS. To date, the mechanism of action of vaccine induced TTS has yet to be elucidated, and a potential role of the Ad26 vector cannot be fully excluded.

Key Safety Findings	Relevance to Human Usage
Toxicity	
Single & repeat-dose toxicity	
Separate studies to determine single-dose toxicity were not performed. Possible signs of acute toxicity were monitored following the first vaccination in the repeat-dose toxicity studies. In the pivotal and supportive repeat-dose toxicity and local tolerance studies in NZW rabbits, various vaccine regimens were tested, which did not show any adverse vaccine-related effects. The 2-dose heterologous regimen of Ad26.ZEBOV and MVA-BN-Filo that is approved for human use was well tolerated when administered to rabbits by intramuscular injection with a 14-day interval period. The vaccine regimen elicited detectable EBOV GP-specific antibody titers. The vaccination was associated with a local inflammatory reaction at the administration sites, a transient systemic inflammatory response (reflected by increases in fibrinogen, C-reactive protein, and	Vaccine regimens of Ad26.ZEBOV (or Ad26.Filo which included Ad26.ZEBOV) and MVA-BN-Filo did not induce any vaccine-related adverse effects in the nonclinical safety studies. All vaccine-related effects were considered to reflect a normal, physiological response associated with vaccination. There were no findings observed that would raise a safety concern for the use of these vaccines or vaccine regimens in humans. The Ad26.ZEBOV and MVA-BN-Filo vaccine dose levels tested in the pivotal and supportive repeat-dose toxicity and local tolerance studies were at least equal to the recommended human dose level for Ad26.ZEBOV ($5x10^{10}$ virus particles [vp]) and MVA-BN-Filo ($1x10^{8}$ Inf.U), hence full human doses were tested. In the supportive repeat-dose toxicity and local tolerance study with Ad26.Filo, a dose level up to $1.2x10^{11}$ vp was tested. Considering that Ad26.Filo (a trivalent mixture of Ad26.ZEBOV with 2 other

Key Safety Findings	Relevance to Human Usage
globulin), and microscopic immunostimulatory findings of increased lymphoid cellularity and/or germinal centers in the draining (iliac) lymph nodes and spleen. The findings were noted to be recovering 2 weeks after the second vaccination, and were considered to reflect a normal, physiological response associated with vaccination. There were no effects noted that were considered to be adverse. In the supportive repeat-dose toxicity and local tolerance studies, either regimens of MVA-BN-Filo alone or of MVA-BN-Filo and a multivalent Ad26.Filo vaccine (which includes Ad26.ZEBOV) were tested in NZW rabbits. In the supportive study with MVA-BN-Filo alone, 4 subcutaneous injections of MVA-BN-Filo were administered with a 7-day interval. In the supportive study with MVA-BN-Filo and Ad26.Filo, various 3-dose intramuscular regimens were tested with a 2-week interval between the injections. This study included a sequential Ad26.Filo, MVA-BN-Filo, Ad26.Filo regimen. Also, in these supportive toxicology studies, no adverse vaccine-related effects were observed.	Ad26 vectors in a 1:1:1 ratio) was tested at a dose level of $1.2x10^{11}$ vp, it implies that Ad26.ZEBOV was dosed close to the full human dose level of $5x10^{10}$ vp in the supportive study with Ad26.Filo. The supportive study with MVA-BN-Filo and Ad26.Filo included a sequential Ad26.Filo, MVA-BN-Filo, Ad26.Filo regimen, and is considered to cover for the booster vaccination with Ad26.ZEBOV that may be administered to individuals who have previously completed the 2-dose primary vaccination regimen (ie, a first dose of Ad26.ZEBOV followed by a second dose of MVA-BN-Filo). In this context, it is noted that available toxicity studies with various Ad26-based vaccines showed a largely similar safety profile, irrespective of the specific antigen that was encoded by the vector.
Reproductive toxicity	
General toxicity studies have not revealed any effects on male sex organs that would impair male fertility. Aspects of female fertility were evaluated as part of the EF-PPND study. In this study, there was no adverse effect of Ad26.ZEBOV or MVA-BN-Filo on reproductive performance, fertility, litter data, or on parturition.	Vaccination with Ad26.ZEBOV or MVA-BN-Filo is unlikely to adversely affect male or female fertility. The Ad26.ZEBOV and MVA-BN-Filo vaccine dose levels tested in the EF-PPND study were at least equal to the recommended human dose level for Ad26.ZEBOV ($5x10^{10}$ vp) and MVA-BN-Filo ($1x10^{8}$ Inf.U), hence full human doses were tested.
Developmental toxicity	
In the EF-PPND study, there was no adverse effect of Ad26.ZEBOV or MVA-BN-Filo on fetal body weights, external, visceral, and skeletal evaluations, or on postnatal development of the offspring. EBOV GP-specific maternal antibodies were transferred to the fetuses.	The available nonclinical data do not indicate any harmful effects with respect to pregnancy, embryonic/fetal development, parturition, or postnatal development. It was shown that EBOV GP-specific maternal antibodies were transferred to the fetuses. This profile is expected to be similar in humans. The clinical significance of maternal antibody transfer to the fetus is unknown.

Key Safety Findings	Relevance to Human Usage
Genotoxicity	
In accordance with the WHO Guidelines on Nonclinical Evaluation of Vaccines (WHO 2005), no genotoxicity studies were performed for Ad26.ZEBOV or MVA-BN-Filo.	Ad26.ZEBOV and MVA-BN-Filo are not expected to be genotoxic in humans.
Carcinogenicity	
In accordance with the WHO Guidelines on Nonclinical Evaluation of Vaccines (WHO 2005), no carcinogenicity testing was performed for Ad26.ZEBOV or MVA-BN-Filo.	Ad26.ZEBOV and MVA-BN-filo are not expected to be carcinogenic in humans.
Juvenile toxicity	
Studies in juvenile animals were not performed.	The available toxicity studies are considered to provide sufficient assurance of safety regarding possible effects associated with an immunological/inflammatory response to the vaccine components in children aged ≥1 year. There were no findings that would indicate a concern for the use of the vaccine regimen in children aged ≥1 year.
Safety pharmacology	
Safety pharmacology studies have not been conducted.	Data from the repeat-dose toxicity studies (including detailed clinical examinations) do not suggest that the vaccine regimen may affect physiological functions (eg, central nervous system, respiratory, cardiovascular, and renal functions) other than those of the immune system.
Other toxicity-related information or data	
Nonclinical biodistribution studies in NZW rabbits showed a limited distribution profile of the Ad26 and MVA-BN vectors following intramuscular injection. In addition, clearance (ie, reflected by a downward trend in number of positive tissues and vector copies over time, to levels close to or below the detected limit) was observed within 7 days for MVA-BN or 90 to 180 days for Ad26.	The Ad26 and MVA vectors are not expected to replicate and/or persist in the tissues following intramuscular injection.

Summary of Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

The clinical development plan of Ad26.ZEBOV and MVA-BN-Filo aimed to develop a 2-dose heterologous vaccine regimen for prevention of EVD caused by EBOV in adults, including HIV-infected individuals, and adolescents and children 1 to 17 years of age.

Several vaccine regimens were tested in the course of the clinical development, assessing homologous and heterologous regimens with different vaccine sequences, dose levels, and intervals between doses.

The Phase 1 trials assessed the preliminary safety and immunogenicity of various vaccine sequences (ie, homologous versus heterologous and Ad26.ZEBOV, MVA-BN-Filo versus MVA-BN-Filo, Ad26.ZEBOV), intervals (ranging from 7 to 56 days), and dose levels in order to select the regimen for further evaluation. The Phase 1 program was conducted in healthy adults aged 18 to 50 years, in Europe, the United States, and Africa, and consisted of 4 VAC52150 trials (EBL1001, EBL1002, EBL1003, EBL1004) and Trial VAC69120FLV1001. Trial FLV1001 assessed the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen in the 56-day interval as control for the multivalent filovirus vaccine regimen (Ad26.Filo, MVA-BN-Filo). Only data from this Ad26.ZEBOV, MVA-BN-Filo control arm are included in this European Union Risk Management Plan (EU-RMP), as Ad26.Filo is not part of the approved vaccine regimen.

The purpose of the Phase 2 (EBL2001, EBL2002, EBL2003) and Phase 3 trials (EBL3001, EBL3002, EBL3003) was to confirm the safety and immunogenicity of the selected regimen, enlarge the safety database, and expand the population to include HIV-infected adults with infection controlled by highly active antiretroviral therapy (HAART), adolescents (12-17 years), and children in 2 age cohorts (1-3 years and 4-11 years). All Phase 2 and Phase 3 trials focused on the selected Ad26.ZEBOV, MVA-BN-Filo vaccine regimen, except for Phase 2 Trial EBL2003 which also assessed the reverse sequence (MVA-BN-Filo, Ad26.ZEBOV). Intervals between vaccine doses that were tested included the 56-day interval, as well as shorter (14-day and 28-day) and longer (84-day) intervals. Two of the Phase 3 trials were conducted in support of the manufacturing process (ie, to support specification settings for potency and to assess manufacturing consistency). The Phase 2 and 3 trials took place in Europe, the United States, and Africa.

An Ad26.ZEBOV booster dose was administered 1 or 2 years after initial vaccination in participants from trials EBL1002, EBL2002, and EBL3001, with the aim to evaluate the presence of immune memory and the potential benefit of a booster dose for administration before likely Ebola virus exposure (referred to as ‘pre-exposure’ booster).

The vaccine dose levels tested were $5x10^{10}$ vp for Ad26.ZEBOV and $1x10^{8}$ $TCID_{50}$ (50% tissue culture infective dose) (used in Phase 1 trials) or $1x10^{8}$ Inf.U (corresponding to $1x10^{8}$ $TCID_{50}$;

used in Phase 2 and 3 trials) for MVA-BN-Filo. Higher dose levels were tested in EBL1002 (Ad26.ZEBOV at $1x10^{11}$ vp and MVA-BN-Filo at $4.4x10^{8}$ $TCID_{50}$), and lower dose levels were tested in EBL3002 (down to Ad26.ZEBOV at $0.8x10^{10}$ or $2x10^{10}$ vp and MVA-BN-Filo at $5x10^{7}$ Inf.U).

All clinical trials were randomized and controlled (placebo or active control), except for the uncontrolled group in Trial EBL1001, the open-label Cohort 1 in Trial EBL2001, and the open-label Stage 1 in Trial EBL3001. All clinical trials were conducted in an observer-blind or double-blind fashion, except for the uncontrolled/open-label groups mentioned above.

The following completed clinical trials are included in this EU-RMP for characterization of exposure and safety:

- 5 Phase 1 trials: EBL1001, EBL1002, EBL1003, EBL1004, and FLV1001
- 3 Phase 2 trials: EBL2001, EBL2002, and EBL2003[1]
- 3 Phase 3 trials: EBL3001[2], EBL3002, and EBL3003

In addition, pregnancy data from the completed MAH-sponsored trials (see above), completed collaborative trial (EBL1005), and ongoing trials (EBL1007, EBL1008, EBL2004, EBL2009, EBL3005, and EBL4001) are included up to the cut-off date of 12 August 2019 (ie, at the time of the marketing authorization). EBL1005 and all the ongoing Phase 1 (healthy adults) and Phase 2 (healthy or HIV-infected adults and/or adolescents and children) trials are randomized, uncontrolled or placebo-controlled, and double-blind, except for EBL2009 which is a non-randomized, open-label trial. The ongoing Phase 3 and 4 trials are observational, long-term trials including adults, children, pregnant women, and infants born to vaccinated female participants.

The clinical trial exposure and safety data of the completed MAH sponsored trials presented in this EU-RMP are pooled as follows:

- The **primary adult pooling** and **pediatric pooling** include all available data from adults (both healthy and HIV-infected) and adolescents and children, respectively, who were enrolled to receive the selected 2-dose heterologous vaccine regimen, ie, Ad26.ZEBOV (Dose 1, $5x10^{10}$ vp) followed by MVA-BN-Filo (Dose 2, $1x10^{8}$ Inf.U) with an interval of at least 28 days between doses. This pooling contains data from the controlled as well as open-label arms of the trials. The primary adult pooling included 2,756 adults and the pediatric pooling included 839 adolescents and children 1 to 17 years of age.
- The **extended adult pooling** includes all available data of the primary adult pooling, supplemented with the data from adults who received other vaccine sequences, intervals, and dose levels (ie, adults who were randomized to receive Ad26.ZEBOV only, lower or higher

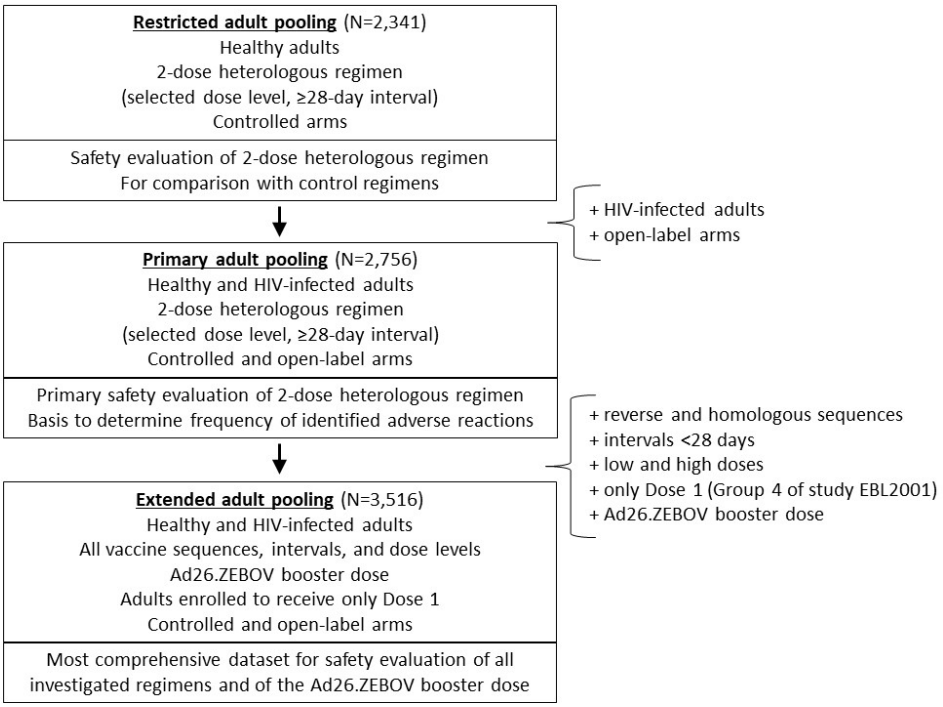
[1] Study EBL2003 was considered ongoing at the cut-off date of 12 August 2019 (ie, the time of marketing authorization), because not all immunogenicity data were available. However, all relevant safety data for this study were available and were included in the EU-RMP.

[2] Study EBL3001 was completed for adults. The vaccination phase for adolescents and children (1-17 years) was also completed, but the follow-up phase was ongoing at the cut-off date of 12 August 2019 (ie, the time of marketing authorization). However, all relevant data for this study were available and were included in the EU-RMP.

dose levels of Ad26.ZEBOV and/or MVA-BN-Filo, homologous vaccine regimens [Ad26.ZEBOV followed by Ad26.ZEBOV or MVA-BN-Filo followed by MVA-BN-Filo], MVA-BN-Filo as Dose 1 regardless of the interval between the 2 doses, and Ad26.ZEBOV followed by MVA-BN-Filo with an interval of less than 28 days between the doses). The extended adult pooling included 3,516 adults.

Data from participants who were enrolled to receive a 2-dose vaccine regimen but missed the second dose were also included in the poolings. All different poolings also include data from participants enrolled to receive the control regimens (ie, placebo control [placebo, placebo] or active control [MenACWY, placebo]).

The above presented poolings are derived from the safety pooling analysis strategy, which includes 1 additional main safety pooling, ie, the restricted adult pooling (similar to the primary adult pooling but excluding HIV-infected adults and open-label arms). In addition to the 4 main safety poolings, a fifth adult pooling analysis, ie, the pooling for adverse reaction identification, is used to identify adverse reactions in the adult population and is based on the dataset of the primary adult pooling excluding data from the open-label arms. A schematic overview of the safety pooling analysis strategy and the scope of each adult main pooling is presented below.



The clinical trial exposure data include data for all participants who received at least 1 dose of study vaccine and including those who received the wrong dose[1].

[1] In the pediatric pooling, 1 participant (12-17 years) was erroneously dosed. The participant received Ad26.ZEBOV as Dose 1 but erroneously received placebo as Dose 2 (instead of MVA-BN-Filo). Therefore, the pediatric pooling used for characterization of exposure consisted of 650 participants who were to receive the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen, while the pediatric pooling used for characterization of safety consisted of 649 participants.

Exposure data (Sections SIII.2 and SIV.3) are summarized and presented by dose. Safety data (Section SIV.3) are summarized and presented by vaccine regimen.

SIII.2. Clinical Trial Exposure

Exposure in the Primary Adult Pooling and in the Pediatric Pooling

Adult Population

The primary adult pooling includes 11 trials:

- Trials EBL1001, EBL1002, EBL1003, EBL1004, FLV1001
- Trials EBL2001, EBL2002, EBL2003
- Trials EBL3001, EBL3002, EBL3003

A total of 2,756 participants are included in this pooling of which 2,253 (1,974 healthy and 279 HIV-infected) participants were enrolled to receive the Ad26.ZEBOV, MVA-BN-Filo regimen at the selected dose level (ie, $5x10^{10}$ vp for Ad26.ZEBOV and $1x10^{8}$ Inf.U for MVA-BN-Filo) with an interval of at least 28 days between the doses, and 503 (440 healthy and 63 HIV-infected) participants were enrolled to receive the control regimen (placebo [N=401] or active control [N=102]).

Exposure to Ad26.ZEBOV, MVA-BN-Filo, and matching controls (placebo and MenACWY) in the primary adult pooling is summarized in Tables SIII.1 through SIII.4 for all participants by dose (and by HIV status), by age group, by sex, and by race.

Table SIII.1: Exposure to Study Vaccine (Primary Adult Pooling)

	Ad26.ZEBOV	MVA-BN-Filo	Placebo	MenACWY*	All Participants
Total number of doses administered, N (%)[a]	2,368	2,034	870	102	5,374
Participants receiving					
Dose 1	2,253 (95.1%)	0	401 (46.1%)	102 (100%)	2,756 (51.3%)
Dose 2	0	2,034 (100%)	452 (52%)	0	2,486 (46.3%)
Dose 3**	115 (4.9%)	0	17 (2%)	0	132 (2.5%)
Participant Population, N (%)[b]	2,253	2,034	487	102	2,756
Healthy Participants	1,974 (87.6%)	1,757 (86.4%)	424 (87.1%)	102 (100%)	2,414 (87.6%)
HIV-infected Participants	279 (12.4%)	277 (13.6%)	63 (12.9%)	0	342 (12.4%)

[a] N (%): total number of doses administered for a particular vaccine (percentage of doses given as Dose 1, Dose 2, or booster dose [Dose 3]).

[b] N (%): total number of participants that received at least 1 dose of a particular vaccine (percentage of participants in a particular category).

* MenACWY: active control present in EBL3001 only.

** Participants who received a booster dose 1 or 2 years after completing initial vaccination with the selected vaccine regimen are part of the primary adult pooling, however safety data of the booster dose are not included in this pooling and are therefore indicated in grey.

Adapted from: [TRMPEX01-P.RTF] [/SAS/Z VAC52150/VAC52150ZSCS/FILES/RE/RMP2019/PROGRAMS/OBJECT SERVER]
08JUL2019, 12:26

Table SIII.2: Exposure to Study Vaccine by Age Group (Primary Adult Pooling)

	Ad26.ZEBOV	MVA-BN-Filo	Placebo	MenACWY*	All Participants
Age, N	2,253	2,034	487	102	2,756
18-50 years	2,037 (90.4%)	1,844 (90.7%)	449 (92.2%)	94 (92.2%)	2,501 (90.7%)
51-64 years	203 (9%)	178 (8.8%)	35 (7.2%)	7 (6.9%)	238 (8.6%)
>64 years	13 (0.6%)	12 (0.6%)	3 (0.6%)	1 (1%)	17 (0.6%)

* MenACWY: active control present in EBL3001 only.
N= number of participants
[TRMPEX02-N-P.RTF] [/SAS/Z_VAC52150/VAC52150ZSCS/FILES/RE/RMP2019/PROGRAMS/OBJECT SERVER] 19AUG2019, 11:41

Table SIII.3: Exposure to Study Vaccine by Sex (Primary Adult Pooling)

	Ad26.ZEBOV	MVA-BN-Filo	Placebo	MenACWY*	All Participants
Sex, N	2,253	2,034	487	102	2,756
Female	898 (39.9%)	822 (40.4%)	210 (43.1%)	22 (21.6%)	1,113 (40.4%)
Male	1,355 (60.1%)	1,212 (59.6%)	277 (56.9%)	80 (78.4%)	1,643 (59.6%)

* MenACWY: active control present in EBL3001 only.
N= number of participants
[TRMPEX03-P.RTF] [/SAS/Z_VAC52150/VAC52150ZSCS/FILES/RE/RMP2019/PROGRAMS/OBJECT SERVER] 08JUL2019, 12:26

Table SIII.4: Exposure to Study Vaccine by Race (Primary Adult Pooling)

	Ad26.ZEBOV	MVA-BN-Filo	Placebo	MenACWY*	All Participants
Race, N	2,253	2,034	487	102	2,756
Asian	23 (1%)	18 (0.9%)	5 (1%)	0	28 (1%)
Black or African American	1,556 (69.1%)	1,448 (71.2%)	343 (70.4%)	102 (100%)	1,915 (69.5%)
White	645 (28.6%)	542 (26.6%)	135 (27.7%)	0	780 (28.3%)
Other	29 (1.3%)	26 (1.3%)	4 (0.8%)	0	33 (1.2%)

* MenACWY: active control present in EBL3001 only.
N= number of participants
[TRMPEX04-P.RTF] [/SAS/Z_VAC52150/VAC52150ZSCS/FILES/RE/RMP2019/PROGRAMS/OBJECT SERVER] 08JUL2019, 12:26

Pediatric Population

The pediatric pooling includes 2 trials:

- Trial EBL2002
- Trial EBL3001

A total of 839 participants are included in this pooling of which 650 participants were enrolled to receive the Ad26.ZEBOV, MVA-BN-Filo regimen at the selected dose level (ie, $5x10^{10}$ vp for Ad26.ZEBOV and $1x10^{8}$ Inf.U for MVA-BN-Filo) with an interval of at least 28 days between the doses, and 189 participants were enrolled to receive the control regimen (placebo [N=45] or active control [N=144]).

Exposure to Ad26.ZEBOV, MVA-BN-Filo, and matching controls (placebo and MenACWY) in the pediatric pooling is summarized in Tables SIII.5 through SIII.8 for all participants by dose, by age group, by sex, and by race.

Table SIII.5: Exposure to Study Vaccine (Pediatric Pooling)

	Ad26.ZEBOV	MVA-BN-Filo	Placebo	MenACWY*	All Participants
Total number of doses administered, N (%)[a]	650	645	231	144	1,670
Participants receiving					
Dose 1	650 (100%)	0	45 (19.5%)	144 (100%)	839 (50.2%)
Dose 2	0	645 (100%)	186 (80.5%)	0	831 (49.8%)
Participant Population, N (%)[b]	650	645	188	144	839
Healthy Participants	650 (100%)	645 (100%)	188 (100%)	144 (100%)	839 (100%)

[a] N (%): total number of doses administered for a particular vaccine (percentage of doses given as Dose 1 or Dose 2.
[b] N (%): total number of participants that received at least 1 dose of a particular vaccine (percentage of participants in a particular category).
* MenACWY: active control present in EBL3001 only.

Adapted from: [TRMPEX01-PED.RTF] [/SAS/Z VAC52150/VAC52150ZSCS/FILES/RE/RMP2019/PROGRAMS/OBJECT SERVER] 08JUL2019, 12:26

Table SIII.6: Exposure to Study Vaccine by Age Group (Pediatric Pooling)

	Ad26.ZEBOV	MVA-BN-Filo	Placebo	MenACWY*	All Participants
Age, N	650	645	188	144	839
1-3 years	144 (22.2%)	143 (22.2%)	48 (25.5%)	48 (33.3%)	192 (22.9%)
4-11 years	252 (38.8%)	251 (38.9%)	72 (38.3%)	48 (33.3%)	324 (38.6%)
12-17 years	254 (39.1%)	251 (38.9%)	68 (36.2%)	48 (33.3%)	323 (38.5%)

* MenACWY: active control present in EBL3001 only.
N= number of participants

[TRMPEX02-PED.RTF] [/SAS/Z_VAC52150/VAC52150ZSCS/FILES/RE/RMP2019/PROGRAMS/OBJECT SERVER] 08JUL2019, 12:26

Table SIII.7: Exposure to Study Vaccine by Sex (Pediatric Pooling)

	Ad26.ZEBOV	MVA-BN-Filo	Placebo	MenACWY*	All Participants
Sex, N	650	645	188	144	839
Female	316 (48.6%)	311 (48.2%)	88 (46.8%)	68 (47.2%)	403 (48%)
Male	334 (51.4%)	334 (51.8%)	100 (53.2%)	76 (52.8%)	436 (52%)

* MenACWY: active control present in EBL3001 only.
N= number of participants

[TRMPEX03-PED.RTF] [/SAS/Z_VAC52150/VAC52150ZSCS/FILES/RE/RMP2019/PROGRAMS/OBJECT SERVER] 08JUL2019, 12:26

Table SIII.8: Exposure to Study Vaccine by Race (Pediatric Pooling)

	Ad26.ZEBOV	MVA-BN-Filo	Placebo	MenACWY*	All Participants
Race, N	650	645	188	144	839
Black or African American	649 (99.8%)	644 (99.8%)	186 (98.9%)	142 (98.6%)	836 (99.6%)
White	1 (0.2%)	1 (0.2%)	2 (1.1%)	2 (1.4%)	3 (0.4%)

* MenACWY: active control present in EBL3001 only.
N= number of participants

[TRMPEX04-PED.RTF] [/SAS/Z_VAC52150/VAC52150ZSCS/FILES/RE/RMP2019/PROGRAMS/OBJECT SERVER] 08JUL2019, 12:26

Exposure in the Extended Adult Pooling

The extended adult pooling includes 11 trials:

- Trials EBL1001, EBL1002, EBL1003, EBL1004, FLV1001
- Trials EBL2001, EBL2002, EBL2003
- Trials EBL3001, EBL3002, EBL3003

A total of 3,516 participants are included in this pooling of which 2,935 (2,596 healthy and 339 HIV-infected) participants were enrolled to receive Ad26.ZEBOV or MVA-BN-Filo at all vaccine sequences, intervals, and dose levels tested, and 581 (503 healthy and 78 HIV-infected) participants were enrolled to receive the control regimen (placebo [N=479] or active control [N=102]).

Exposure to Ad26.ZEBOV (different dose levels), MVA-BN-Filo (different dose levels), and matching controls (placebo and MenACWY) in the extended adult pooling is summarized in Tables SIII.9 through SIII.12 for all participants by dose (and by HIV status), by age group, by sex, and by race.

Table SIII.9: Exposure to Study Vaccine (Extended Adult Pooling)

	Ad26-LLD	Ad26-LD	Ad26	Ad26-HD	MVA-LD	MVA	MVA-HD	Men-ACWY*	Placebo	All Participants
Total number of doses administered, N (%)[a]	150	150	2,777	25	287	2,376	29	102	1,023	6,919
Participants receiving Dose 1	150 (100%)	150 (100%)	2,305 (83%)	15 (60%)	0	314 (13.2%)	1 (3.4%)	102 (100%)	479 (46.8%)	3,516 (50.8%)
Dose 2	0	0	305 (11%)	0	287 (100%)	2,055 (86.5%)	28 (96.6%)	0	527 (51.5%)	3,202 (46.3%)
Dose 3	0	0	167 (6%)	10 (40%)	0	7 (0.3%)	0	0	17 (1.7%)	201 (2.9%)
Participant Population, N (%)[b]	150	150	2,608	15	287	2,367	29	102	565	3,516
Healthy Participants	150 (100%)	150 (100%)	2,271 (87.1%)	15 (100%)	287 (100%)	2,030 (85.8%)	29 (100%)	102 (100%)	487 (86.2%)	3,099 (88.1%)
HIV-infected Participants	0	0	337 (12.9%)	0	0	337 (14.2%)	0	0	78 (13.8%)	417 (11.9%)

Ad26: Ad26.ZEBOV($5x10^{10}$ vp); Ad26-HD: Ad26.ZEBOV($1x10^{11}$ vp); Ad26-LD: Ad26.ZEBOV($2x10^{10}$ vp);
Ad26-LLD: Ad26.ZEBOV($0.8x10^{10}$ vp); MVA: MVA-BN-Filo($1x10^{8}$ Inf U); MVA-LD: MVA-BN-Filo($5x10^{7}$ Inf U);
MVA-HD: MVA-BN-Filo($4.4x10^{8}$ Inf U).

[a] N (%): total number of doses administered for a particular vaccine (percentage of doses given as Dose 1, Dose 2, or booster dose [Dose 3]).

[b] N (%): total number of participants that received at least 1 dose of a particular vaccine (percentage of participants in a particular category).

* MenACWY: active control present in EBL3001 only.

Adapted from: [TRMPEX01-E.RTF] [/SAS/Z_VAC52150/VAC52150ZSCS/FILES/RE/RMP2019/PROGRAMS/OBJECT SERVER] 08JUL2019, 12:26

Table SIII.10: Exposure to Study Vaccine by Age Group (Extended Adult Pooling)

	Ad26-LLD	Ad26-LD	Ad26	Ad26-HD	MVA-LD	MVA	MVA-HD	Men-ACWY*	Placebo	All Participants
Age, N	150	150	2,608	15	287	2,367	29	102	565	3,516
18-50 years	150 (100%)	150 (100%)	2,361 (90.5%)	15 (100%)	287 (100%)	2,148 (90.7%)	29 (100%)	94 (92.2%)	518 (91.7%)	3,221 (91.6%)
51-64 years	0	0	230 (8.8%)	0	0	203 (8.6%)	0	7 (6.9%)	44 (7.8%)	274 (7.8%)
>64 years	0	0	17 (0.7%)	0	0	16 (0.7%)	0	1 (1%)	3 (0.5%)	21 (0.6%)

Ad26: Ad26.ZEBOV($5x10^{10}$ vp); Ad26-HD: Ad26.ZEBOV($1x10^{11}$ vp); Ad26-LD: Ad26.ZEBOV($2x10^{10}$ vp);
Ad26-LLD: Ad26.ZEBOV($0.8x10^{10}$ vp); MVA: MVA-BN-Filo($1x10^{8}$ Inf U); MVA-LD: MVA-BN-Filo($5x10^{7}$ Inf U);
MVA-HD: MVA-BN-Filo($4.4x10^{8}$ Inf U).
*MenACWY: active control present in EBL3001 only.
N= number of participants

Adapted from: [TRMPEX02-N-E.RTF] [/SAS/Z_VAC52150/VAC52150ZSCS/FILES/RE/RMP2019/PROGRAMS/OBJECT SERVER] 19AUG2019, 11:41

Table SIII.11: Exposure to Study Vaccine by Sex (Extended Adult Pooling)

	Ad26-LLD	Ad26-LD	Ad26	Ad26-HD	MVA-LD	MVA	MVA-HD	Men-ACWY*	Placebo	All Participants
Sex, N	150	150	2,608	15	287	2367	29	102	565	3,516
Female	83 (55.3%)	83 (55.3%)	1,048 (40.2%)	8 (53.3%)	164 (57.1%)	966 (40.8%)	12 (41.4%)	22 (21.6%)	253 (44.8%)	1,486 (42.3%)
Male	67 (44.7%)	67 (44.7%)	1,560 (59.8%)	7 (46.7%)	123 (42.9%)	1,401 (59.2%)	17 (58.6%)	80 (78.4%)	312 (55.2%)	2,030 (57.7%)

Ad26: Ad26.ZEBOV($5x10^{10}$ vp); Ad26-HD: Ad26.ZEBOV($1x10^{11}$ vp); Ad26-LD: Ad26.ZEBOV($2x10^{10}$ vp);
Ad26-LLD: Ad26.ZEBOV($0.8x10^{10}$ vp); MVA: MVA-BN-Filo($1x10^{8}$ Inf U); MVA-LD: MVA-BN-Filo($5x10^{7}$ Inf U);
MVA-HD: MVA-BN-Filo($4.4x10^{8}$ Inf U).
*MenACWY: active control present in EBL3001 only.
N= number of participants

Adapted from: [TRMPEX03-E.RTF] [/SAS/Z_VAC52150/VAC52150ZSCS/FILES/RE/RMP2019/PROGRAMS/OBJECT SERVER] 08JUL2019, 12:26

Table SIII.12: Exposure to Study Vaccine by Race (Extended Adult Pooling)

	Ad26-LLD	Ad26-LD	Ad26	Ad26-HD	MVA-LD	MVA	MVA-HD	Men-ACWY*	Placebo	All Participants
Race, N	150	150	2,608	15	287	2,367	29	102	565	3,516
Asian	1 (0.7%)	2 (1.3%)	26 (1%)	1 (6.7%)	3 (1%)	21 (0.9%)	1 (3.4%)	0	6 (1.1%)	36 (1%)
Black or African American	29 (19.3%)	26 (17.3%)	1,766 (67.7%)	4 (26.7%)	52 (18.1%)	1,657 (70%)	7 (24.1%)	102 (100%)	395 (69.9%)	2,244 (63.8%)
White	118 (78.7%)	120 (80%)	778 (29.8%)	9 (60%)	228 (79.4%)	655 (27.7%)	19 (65.5%)	0	160 (28.3%)	1,189 (33.8%)
Other	2 (1.3%)	2 (1.3%)	38 (1.5%)	1 (6.7%)	4 (1.4%)	34 (1.4%)	2 (6.9%)	0	4 (0.7%)	47 (1.3%)

Ad26: Ad26.ZEBOV($5x10^{10}$ vp); Ad26-HD: Ad26.ZEBOV($1x10^{11}$ vp); Ad26-LD: Ad26.ZEBOV($2x10^{10}$ vp);
Ad26-LLD: Ad26.ZEBOV($0.8x10^{10}$ vp); MVA: MVA-BN-Filo($1x10^{8}$ Inf U); MVA-LD: MVA-BN-Filo($5x10^{7}$ Inf U);
MVA-HD: MVA-BN-Filo($4.4x10^{8}$ Inf U).
*MenACWY: active control present in EBL3001 only.
N= number of participants

Adapted from: [TRMPEX04-E.RTF] [/SAS/Z_VAC52150/VAC52150ZSCS/FILES/RE/RMP2019/PROGRAMS/OBJECT SERVER] 08JUL2019, 12:26

PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Known allergy or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine products (including any of the constituents of the study vaccines)**
Reason for being an exclusion criterion	These individuals were excluded from clinical trials to avoid potentially severe and life-threatening allergic/hypersensitivity reactions. In addition, anaphylaxis is always considered a risk with parenterally administered foreign proteins.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Standard medical practice for any vaccine includes contraindication of administration of the vaccines in case of known allergy to their components and for the vaccinator to be ready to immediately treat any possible severe allergic reaction such as anaphylaxis. The Summary of Product Characteristics (SmPC) Section 4.3 states that Ad26.ZEBOV and MVA-BN-Filo should not be used in individuals with hypersensitivity to the active substance or to any of their excipients, or to trace residues (chicken or egg protein and gentamicin) of MVA-BN-Filo. Risk minimization activities regarding close observation following vaccination for the early signs of anaphylaxis or anaphylactoid reactions and being prepared for appropriate medical treatment and supervision in case of rare anaphylactic reactions are included in SmPC Section 4.4.

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 2	**A woman who is pregnant, or planning to become pregnant while enrolled in the trial** - **or within 3 months after the second vaccination*** **Or:** - **until at least 3 months after the first vaccination or up to 1 month after the second vaccination, whichever takes longer**** *** For blinded trials where either Ad26.ZEBOV or MVA-BN-Filo was administered as first or second dose.** **** For blinded trials where Ad26.ZEBOV was administered as first dose and MVA-BN-Filo as second dose.**
Reason for being an exclusion criterion	Per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, pregnant women should normally be excluded from clinical trials.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Use during pregnancy is no longer considered missing information based on the availability of pregnancy data from Trials EBL3010 and EBL3008 and from the post-approval vaccination campaigns UMURINZI/EBL4002 and EBL4004. Pregnancy data from Trial EBL3008 and from the post-approval vaccination campaigns did not reveal a vaccine-associated risk of congenital anomalies or feto/neonatal toxicity. In Trial EBL3010, the percentage of women with any adverse maternal/fetal or neonatal/infant outcome was similar in vaccinated pregnant women versus unvaccinated pregnant women. There was a numerical imbalance in cases of neonatal death, although the rates were below the background neonatal death rate. SmPC Section 4.6 states that it is preferred to only use Ad26.ZEBOV and MVA-BN-Filo during pregnancy if the benefits of immediate vaccination outweigh the potential risks.

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 3	**Breastfeeding women**
Reason for being an exclusion criterion	Breastfeeding women are usually excluded from clinical trials.
Considered to be included as missing information	No
Rationale (if not included as missing information)	No clinical trials have explored transfer of vaccine in breastmilk, however, due to the limited biodistribution observed in nonclinical studies, Ad26.ZEBOV and MVA-BN-Filo are unlikely to be excreted in breastmilk. If a small quantity of vaccine would be excreted in breastmilk, it would not cause infection in the newborn as Ad26.ZEBOV and MVA-BN-Filo are non-replicating (for MVA-BN-Filo non-replicating in human cells) vaccines. SmPC Section 4.6 states as a precautionary measure that it is preferable to avoid vaccination with Ad26.ZEBOV and MVA-BN-Filo during breastfeeding. Nevertheless, considering the severity of EVD, vaccination should not be withheld when there is a clear risk of exposure to Ebola infection.
Criterion 4	**Presence of significant clinical conditions (eg, history of seizure disorders, bleeding/clotting disorders, cardiac disease, (auto)immune disease or deficiency, any spleen disease, active malignancy, poorly controlled asthma, active tuberculosis, or other systemic infections)**
Reason for being an exclusion criterion	These individuals were excluded from the initial clinical trials to obtain unconfounded immunogenicity and safety results, not because specific safety risks were anticipated.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Real world experience of the use of the vaccines in individuals with these conditions will take the place of dedicated investigations in these subpopulations as there is no safety concern anticipated which would preclude use in individuals with these conditions.

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 5	**Receipt of live attenuated vaccines from 30 days before Day 1 to 30 days after the last study vaccination or receipt of any other vaccine from 15 days before to 15 days after any study vaccine**
Reason for being an exclusion criterion	Concomitant vaccination could influence the participant's immune response to either of the vaccines and could confound the safety evaluation.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Ad26.ZEBOV and MVA-BN-Filo are not part of routine immunization schedules, limiting the probability of co-administration. SmPC Section 4.5 states that the safety, immunogenicity, and efficacy of co-administration of Ad26.ZEBOV or MVA-BN-Filo with other vaccines have not been evaluated, and therefore, co-administration is not recommended.
Criterion 6	**Immunosuppressed subjects, either due to medication (eg, cancer chemotherapeutic agents, chronic use of systemic corticosteroids, immunosuppressive therapy for post-organ and/or stem cell transplant) or diseases (eg, cancer)**
Reason for being an exclusion criterion	These individuals were excluded from the initial clinical trials to obtain unconfounded immunogenicity results, not because specific safety risks were anticipated.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Ad26.ZEBOV and MVA-BN-Filo are non-replicating (for MVA-BN-Filo non-replicating in human cells) vaccines, therefore, there are no risks of infection leading to potential adverse clinical outcomes and the safety profile is not expected to be significantly different than in the general population.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions and adverse reactions with a long latency.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	In completed and ongoing clinical trials (EBL1001, EBL1002, EBL1003, EBL1004, EBL1005, EBL1007, EBL1008, FLV1001, EBL2001, EBL2002, EBL2003, EBL2004, EBL2009, EBL3001, EBL3002, EBL3003, EBL3005, and EBL4001), a total of 66 pregnancies were reported after vaccination in female participants up to a cut-off date of 12 August 2019 (ie, at the time of the marketing authorization).
Breastfeeding women	Not included in the clinical development program.
Population with relevant different ethnic origin	Of the 2,253 participants in the primary adult pooling who received Ad26.ZEBOV, 1,556 (69.1%) participants were black or African American, 645 (28.6%) participants were white, 23 (1.0%) participants were Asian, and 29 (1.3%) participants were of another race. Of the 2,034 participants in the primary adult pooling who received MVA-BN-Filo, 1,448 (71.2%) participants were black or African American, 542 (26.6%) participants were white, 18 (0.9%) participants were Asian, and 26 (1.3%) participants were of another race. Of the 650 participants in the pediatric pooling who received Ad26.ZEBOV, 649 (99.8%) participants were black or African American and 1 (0.2%) participant was white. Of the 645 participants in the pediatric pooling who received MVA-BN-Filo, 644 (99.8%) participants were black or African American and 1 (0.2%) participant was white. Of the 2,608 participants in the extended adult pooling who received Ad26.ZEBOV at the selected dose level, 1,766 (67.7%) participants were black or African American, 778 (29.8%) participants were white, 26 (1.0%) participants were Asian, and 38 (1.5%) participants were of another race. Of the 2,367 participants in the extended adult pooling who received MVA-BN-Filo at the selected dose level, 1,657 (70.0%) participants were black or African American, 655 (27.7%) participants were white, 21 (0.9%) participants were Asian, and 34 (1.4%) participants were of another race.
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Pediatric population	Of the 650 participants in the pediatric pooling who received Ad26.ZEBOV, 144 (22.2%) participants were 1 to 3 years of age, 252 (38.8%) were 4 to 11 years of age, and 254 (39.1%) were 12 to 17 years of age. Of the 645

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
	participants in the pediatric pooling who received MVA-BN-Filo, 143 (22.2%) participants were 1 to 3 years of age, 251 (38.9%) were 4 to 11 years of age, and 251 (38.9%) were 12 to 17 years of age.
Elderly	Of the 2,253 participants in the primary adult pooling who received Ad26.ZEBOV, 13 (0.6%) participants were above 64 years of age and 203 (9.0%) participants were 51 to 64 years of age. Of the 2,034 participants in the primary adult pooling who received MVA-BN-Filo, 12 (0.6%) participants were above 64 years of age and 178 (8.8%) participants were 51 to 64 years of age. Of the 2,608 participants in the extended adult pooling who received Ad26.ZEBOV at the selected dose level, 17 (0.7%) participants were above 64 years of age and 230 (8.8%) participants were 51 to 64 years of age. Of the 2,367 participants in the extended adult pooling who received MVA-BN-Filo at the selected dose level, 16 (0.7%) participants were above 64 years of age and 203 (8.6%) participants were 51 to 64 years of age.
Individuals with relevant comorbidities:	
Individuals with hepatic impairment	Not applicable
Individuals with renal impairment	Not applicable
Individuals with cardiovascular impairment	Not applicable
Immunocompromised individuals	Of the 2,253 and 2,034 participants in the primary adult pooling who received respectively Ad26.ZEBOV and MVA-BN-Filo, 279 (12.4%) participants and 277 (13.6%) participants were HIV-infected with CD4+ cell count >200 cells/µL (EBL2003) or >350 cells/µL (EBL2002) (but well controlled through HAART). Of the 2,608 and 2,367 participants in the extended adult pooling who received respectively Ad26.ZEBOV and MVA-BN-Filo at the selected dose level, 337 (12.9%) participants and 337 (14.2%) participants were HIV-infected (but well controlled through HAART). None of the participants in the pediatric pooling was HIV-infected.
Individuals with a disease severity different from inclusion criteria in clinical trials	Not applicable

Use in pregnant women

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Female reproductive toxicity and (aspects of) fertility were assessed in a combined EF-PPND study in the rabbit. There was no adverse effect of Ad26.ZEBOV or MVA-BN-Filo on reproductive performance, fertility, litter data, or on parturition. In addition, there was no adverse effect of vaccination on fetal body weights, external, visceral, and skeletal evaluations, or on postnatal development of the offspring. EBOV GP-specific maternal antibodies were transferred to the fetuses. This profile is expected to be similar in humans. The clinical significance of maternal antibody transfer to the fetus is unknown.

There were no data from the use of Ad26.ZEBOV and MVA-BN-Filo in pregnant women at the time of the marketing authorization (ie, data cut-off date of 12 August 2019). Therefore, 'Use during pregnancy' was included as missing information in the EU-RMP. Since then, data on use in pregnant women has been collected through clinical trials and the post-approval vaccination campaigns (UMURINZI/EBL4002 and EBL4004).

Two completed clinical trials, EBL3010 and EBL3008, included active vaccination of pregnant women. All other Ebola vaccine study protocols had pregnancy restrictions that included being pregnant or planning to become pregnant as an exclusion criterion, with the requirement for use of adequate birth control methods for female participants of childbearing potential. A pregnancy test was systematically performed in these women prior to each study vaccine administration, and women with a positive pregnancy test were excluded from receiving study vaccine. The post-approval vaccination campaign (UMURINZI/EBL4002) also excluded pregnant women. However, participants of UMURINZI/EBL4002 who became pregnant after receiving the first dose or who were inadvertently vaccinated while being pregnant were referred to EBL3010. The pregnant women who did not meet EBL3010 inclusion criteria remained in UMURINZI/EBL4002 and only received their second dose after delivery or after the pregnancy ended. Both EBL3010 and UMURINZI/EBL4002 have been conducted in Rwanda.

A prophylactic vaccination campaign (EBL4004) has been conducted in the Equateur province in the DRC, in an area that has experienced several prior outbreaks. This vaccination campaign was sponsored by the Institut National de Recherche Biomédicale (National Institute of Biomedical Research, DRC).

Trial EBL3010

Trial EBL3010 was a Phase 3, open-label, randomized trial to evaluate the safety, reactogenicity, and immunogenicity of the Ad26.ZEBOV, MVA-BN-Filo vaccination regimen in healthy pregnant women in Rwanda. The trial was included as a category 3 additional pharmacovigilance activity in the EU-RMP to address the missing information 'Use during pregnancy'.

A total of 992 healthy pregnant women received Dose 1 (Ad26.ZEBOV) of the 2-dose heterologous Ebola vaccine regimen during pregnancy, of whom 981 also received Dose 2 (MVA-BN-Filo) during pregnancy. A total of 964 infants were born alive to women who received at least one dose of the study vaccine regimen during pregnancy.

Another 1,020 healthy pregnant women were enrolled in a control group. These women were unvaccinated during pregnancy but eligible to receive the first dose of the study vaccine regimen at the earliest 6 and up to 10 weeks after completion/termination of pregnancy, with the second dose administered 8 weeks later. A total of 981 infants were born alive to women enrolled in the control group.

Pregnancy outcome data was available for 977 women vaccinated during pregnancy and for 1,000 women not vaccinated during pregnancy (control group). In each group, 51 participants were randomized in the first trimester of pregnancy and had available pregnancy outcomes; all 51 participants vaccinated during the first trimester of pregnancy received Dose 1 in the first trimester and Dose 2 in the second trimester.

From randomization to 6 weeks postpartum, adverse maternal/fetal outcomes of special interest as defined by the Brighton Collaboration (ie, maternal death, spontaneous abortion/miscarriage, stillbirth, pathways to preterm birth, pre-eclampsia/eclampsia, antenatal bleeding, and postpartum hemorrhage) were reported in 51/977 (5.2%) of women vaccinated during pregnancy and in 73/1,000 (7.3%) of women in the control group. From birth to 14 weeks of age, adverse neonatal/infant outcomes of special interest as defined by the Brighton Collaboration (ie, congenital anomalies, small for gestational age, low birth weight, preterm birth, neonatal death, and failure to thrive) were reported in 250/964 (25.9%) of infants born to women vaccinated during pregnancy and 249/981 (25.4%) of infants born to women in the control group.

Overall, the percentage of women with any adverse maternal/fetal or neonatal/infant outcome was similar in 977 vaccinated pregnant women (including 51 women who were in the first trimester at randomization) versus 1,000 unvaccinated pregnant women (including 51 women who were in the first trimester at randomization): 0.4% versus 0.5% for spontaneous abortion/miscarriage, 0.9% versus 1.1% for congenital anomalies, 2.7% versus 3.1% for preterm birth, and 4.7% versus 5.0% for low birth weight, respectively. Similar incidences were observed for other outcomes. Twenty-two infant deaths were reported throughout the entire trial: 12/964 (1.2%) infants born to vaccinated pregnant women versus 10/981 (1.0%) born to unvaccinated pregnant women. Amongst these, there was a numerical imbalance in cases of neonatal death (1.1% versus 0.5%), including neonatal deaths related to hypoxic ischemic encephalopathy. These rates are below the background neonatal death rate of 20 per 1,000 live births. Among the 51 pregnant women who were vaccinated during the first trimester, 2 (3.9%) reported a spontaneous abortion/miscarriage and none of the pregnancies resulted in a stillbirth. For the 49 infants born alive, no neonatal deaths and no congenital anomalies were reported. Of the 51 unvaccinated pregnant women who were randomized in the first trimester, none reported a spontaneous abortion/miscarriage and 2 (3.9%) pregnancies resulted in a stillbirth. For the 49 infants born alive, no neonatal deaths and no congenital anomalies were reported.

Trial EBL3008

Trial EBL3008 was a large-scale, non-randomized, open-label Phase 3 trial in which the Ad26.ZEBOV, MVA BN Filo vaccination regimen was evaluated in adults and children aged

≥1 year, including women who reported at least 1 pregnancy during the trial. The trial was sponsored by the London School of Hygiene & Tropical Medicine and conducted in DRC.

Of the 1,238 pregnancies reported during the trial, there were no pregnancy outcome data collected for 69 pregnancies (55 were lost to follow-up, 13 pregnancies were not confirmed during follow-up, and 1 pregnant woman died). Therefore, the full analysis set for pregnancy outcomes was 1,169 pregnancies with a known outcome and conception up to 1 month post Dose 2.

Among the 1,169 pregnancies with a known birth outcome, 55 (4.7%) resulted in a spontaneous abortion/miscarriage, 31 (2.7%) resulted in a stillbirth (including 1 twin pregnancy that resulted in 1 stillbirth), and 1,084 (92.7%) were pregnancies with at least 1 infant born alive. There were 17 (1.5%) twin pregnancies; 16 resulted in 2 live births and 1 resulted in 1 live birth and 1 stillbirth. The number of infants born alive for the analysis of neonatal outcomes was 1,100. Neonatal deaths within 7 days occurred in 11 (1.0%) infants born alive. Amongst 891 infants for whom gestational age could be calculated from an available date of last menstrual period (LMP), 188 (21.1%) were classified as born premature. Five (0.5%) infants were born with a congenital anomaly (1 inguinal hernia, 1 umbilical hernia, 1 congenital anomaly of the tongue, 1 cleft lip, and 1 exomphalos). None of these congenital anomalies were deemed to be related to any study vaccine by the investigator and the MAH. Amongst 1,032 infants born alive with a recorded birth weight, 79 (7.7%) were born with a weight less than 2.5 kg. Amongst 672 infants assumed to be full-term based on available date of LMP (≥37 weeks of gestation), 33 (4.9%) had a low birth weight (<2.5 kg).

For 300 pregnancies, exposure to at least 1 of the study vaccines took place during the first trimester. Of those 300 pregnancies, pregnancy outcome data were available for 283 pregnancies (94.3%). Thirty-seven (13.1%) of these pregnancies resulted in a spontaneous abortion/miscarriage; 238 infants were born alive, none of whom were reported with congenital anomalies. Neonatal death within 7 days was reported in 4 (1.7%) infants, 62 (27.0%) infants were born prematurely, and 25 (10.9%) had a low birth weight. A total of 383 and 438 pregnancies were exposed to at least 1 of the study vaccines during the second and third trimester, respectively.

Post-approval vaccination campaigns

The Company Global Safety Database was searched for medically confirmed and medically unconfirmed cases received cumulatively through 26 September 2023 from the post-approval vaccination campaigns UMURINZI/EBL4002 and EBL4004, which may involve exposure during pregnancy. The following search strategy was used: Pregnancy OR Breastfeeding/Lactation Exposure terms OR (SOC [Event Dictionary]=Congenital, Familial and Genetic Disorders OR SOC [Event Dictionary]=Pregnancy, Puerperium and Perinatal Conditions]) OR (AER Registration - Pregnancy - Classification=Yes) OR (Pregnancy=Yes) OR (Age Group=Foetus OR Age Group=Infant OR Age Group=Neonate) OR (Patient Age in Years <03). Cases which did not

report vaccination during pregnancy or reported vaccination more than 3 months prior to pregnancy or after the reported pregnancy outcome, were not analyzed.

A total of 1,041 unique maternal exposures within 3 months prior to or during the pregnancy were reported. Of these, 1,025 exposures were to Ad26.ZEBOV, 6 were to MVA-BN-Filo, and 10 were to both Ad26.ZEBOV and MVA-BN-Filo before/during the same pregnancy.

There were 1,051 unique pregnancy outcomes for the 1,041 unique pregnancies, including 10 twin pregnancies with outcome of live birth for both infants. Of the 1,051 unique pregnancy outcomes, 765 pregnancies had known outcomes after excluding 283 pregnancies which were ongoing or for which the outcome was unknown and 3 elective abortions. There were no reports of maternal death. Of the 644 infants born alive, there were 2 (0.3%) neonatal deaths and 2 (0.3%) outcomes concerned live birth with a congenital anomaly of cleft palate; in the first case, the mother received the vaccine in the first trimester (gestational age at 3 weeks 4 days), in the second case (a twin pregnancy in which 1 infant had a congenital anomaly and the other had a normal outcome), the mother received the vaccine 28 days prior to the LMP. In both cases, no significant past medical conditions were reported and family history was not provided. A total of 115 spontaneous abortions/miscarriages were reported, which represents a reporting rate of 15.0%. Of these 115 cases, 90 were prospective cases, of which 33 occurred in mothers who were exposed in the first trimester, while most cases occurred in mothers who were exposed to the vaccine within 91 days prior to the LMP (52/90 [57.8%]; in 5 cases, timing of exposure was not reported). Six (0.8%) pregnancies reported an outcome of fetal demise/stillbirth.

Overall, based on the 1,051 unique pregnancy outcomes from the 2 post-approval campaigns, the estimated reporting rate was 15.0% (115/765) for spontaneous abortion/miscarriage and 0.3% (2/644) for congenital anomalies. Among 233 first trimester exposed prospective pregnancies with known outcome, 14.2% (33/233) resulted in spontaneous abortion/miscarriage and 203 infants were born alive, of whom 0.5% (1/203) had at least one congenital anomaly. For the post-approval vaccination campaigns, a report of pregnancy exposure was considered to be prospective if the earliest report of pregnancy contained no pregnancy outcome information.

Conclusion of pregnancy data across the clinical trials and post-approval vaccination campaigns

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The overall incidence of malformations generally detected at birth is approximately 3% of all live births (EMA Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation 2008). In the US general population, the prevalence of major congenital anomalies and spontaneous abortion/miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively (FDA Guidance for Industry: Pregnancy, lactation, and reproductive potential: labeling for human prescription drug and biological products - content and format 2014).

Based on the data from Trials EBL3010 and EBL3008, and the post-approval vaccination campaigns UMURINZI/EBL4002 and EBL4004, 567 prospective pregnancies were exposed to either Ad26.ZEBOV or MVA-BN- Filo, or both during the first trimester and had a known outcome. Among these 567 pregnancies, no congenital anomalies were reported in EBL3010 and

EBL3008, and 1 infant with congenital anomaly (0.5%) was reported in the 2 post-approval campaigns. Spontaneous abortions/miscarriages were reported in 2/51 (3.9%), 37/283 (13.1%) and 33/233 (14.2%) first trimester exposed pregnancies in EBL3010, EBL3008, and the 2 post-approval campaigns, respectively. The incidences of congenital anomalies and spontaneous abortions/miscarriages were within the background rates provided by EMA and FDA. There were more than 1,000 pregnancy outcomes from exposure to the vaccine regimen during the second and third trimester.

Data from Trial EBL3008 and the post-approval vaccination campaigns revealed no vaccine-associated congenital anomalies or feto/neonatal toxicity. In Trial EBL3010, the percentage of women with any adverse maternal/fetal or neonatal/infant outcome was similar in vaccinated pregnant women versus unvaccinated pregnant women. There was a numerical imbalance in cases of neonatal death, although the rates were below the background neonatal death rate. Based on all available data, individual risk and potential benefit should be carefully considered before administering the Ad26.ZEBOV and MVA-BN-Filo vaccination regimen. A recommendation is included in Section 4.6 of the SmPC.

Use during pregnancy is no longer considered missing information.

Use in breastfeeding women

The effect of the study vaccines on a nursing baby is unknown. It is not known whether Ad26.ZEBOV or MVA-BN-Filo are excreted in human milk.

Breastfeeding was an exclusion criterion for vaccination in all clinical trials conducted up to a cut-off date of 12 August 2019 (ie, at the time of the marketing authorization).

The WHO recommends mothers worldwide to exclusively breastfeed infants for the child's first 6 months of life to achieve optimal growth, development, and health. Thereafter, to meet their evolving nutritional requirements, infants should receive nutritionally adequate and safe complementary foods, while continuing to breastfeed for up to 2 years or beyond (WHO 2019d). In some areas where Ebola virus outbreaks happened in the past, inadequate sanitation does represent a risk for stopping breastfeeding, eg, possible use of contaminated water to prepare formula milk. Therefore, a careful benefit/risk assessment should be performed for the individual breastfeeding woman if vaccination with Ad26.ZEBOV, MVA-BN-Filo is considered, as reflected in the SmPC.

The SmPC Section 4.6 states that a risk to the newborns/infants from breastfeeding by vaccinated mothers cannot be excluded. Hence, as a precautionary measure, it is preferable to avoid vaccination with Ad26.ZEBOV and MVA-BN-Filo during breastfeeding. Nevertheless, considering the severity of EVD, vaccination should not be withheld when there is a clear risk of exposure to Ebola infection.

Given the limited biodistribution observed in nonclinical studies, it is considered unlikely that Ad26.ZEBOV or MVA-BN-Filo are excreted in breastmilk in humans. Even if a small quantity of vaccine would be excreted, it would not cause infection in the newborn, as Ad26.ZEBOV and

MVA-BN-Filo are non-replicating (for MVA-BN-Filo non-replicating in human cells) vaccines, containing incomplete viral genomes. There are no additional pharmacovigilance activities to evaluate the use of Ad26.ZEBOV, MVA-BN-Filo in breastfeeding women and the information provided in the SmPC and the package leaflet (PL) is considered sufficient for the purposes of risk communication.

Therefore, use in breastfeeding women is not considered missing information.

Pediatric population

The posology in children aged 1 to <18 years is the same as in adults. The safety and efficacy of the 2-dose primary vaccination regimen and the booster dose have not been established in children <1 year of age.

Infants <1 year of age are less exposed to Ebola virus, especially while they are not yet mobile. They may be protected indirectly through herd immunity, and via vaccination of close contacts during an epidemic. In addition, the administration of the Ebola vaccine regimen to children <1 year of age has the potential to interfere with or compromise established infant immunization schedules. It was thus concluded that vaccinating infants <1 year of age would not bring a significant benefit to this population, and a waiver was granted for infants <1 year of age (Pediatric Investigation Plan [PIP] EMA Decision 28 March 2019: P/0116/2019 [Ad26], P/0117/2019 [MVA]).

However, in view of the high mortality of EVD in young children, the assessment of the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen in the pediatric population is being extended to infants <1 year of age (4-11 months) in Trial EBL2005. Although the incidence of EVD is low in infants, the morbidity and mortality are high.

Under this marketing authorization, the use of Ad26.ZEBOV and MVA-BN-Filo is not indicated for children <1 year of age.

Therefore, use in children <1 year of age is not considered missing information.

Use in subjects with immunosuppression/reduced immune response

The safety and immunogenicity of the vaccine regimen have been assessed in HIV-infected adults with infection controlled through antiretroviral therapy and CD4+ cells >350 cells/µL. In addition, safety data are available for participants with CD4+ cells >200 cells/µL who received the selected regimen although in a shorter interval (EBL2003), with no specific safety concerns. In the HIV-infected groups in clinical trials, the majority of adverse events (AEs) reported post-vaccination were mild (grade 1 or 2) and transient in nature. There were no notable differences between HIV-infected and healthy participants, with regard to reporting frequency or severity of AEs, at any timepoint.

The SmPC Section 4.2 states that no dosage adjustment is required in HIV-infected individuals with infection controlled through antiretroviral therapy.

Safety and immunogenicity of Ad26.ZEBOV and MVA-BN-Filo have not been assessed in immunocompromised individuals, including those receiving immunosuppressive therapy. HIV-infected adults on antiretroviral therapy without signs of immunodeficiency were assessed.

Given the fact that Ad26.ZEBOV and MVA-BN-Filo are non-replicating (for MVA-BN-Filo non-replicating in human cells) vaccines, the safety profile of Ad26.ZEBOV and MVA-BN-Filo when used in immunocompromised individuals is not expected to differ from that in the general population, with no specific safety concerns. No further evaluation as part of the Pharmacovigilance Plan to characterize the use of Ad26.ZEBOV, MVA-BN-Filo in this population is planned and the information provided in the SmPC and the PL is considered sufficient for the purposes of risk communication.

Therefore, use in subjects with immunosuppression/reduced immune response is not considered missing information.

Summary of Missing Information Due to Limitations of the Clinical Trial Program

None

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

A conditional approval under an exceptional emergency situation was granted for the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen by the Rwanda FDA on 27 September 2019. This approval was subsequently extended for an additional year. Consequently, the UMURINZI Ebola Vaccination Campaign (EBL4002) was launched, which was a post-approval vaccination campaign performed under the auspices of the Rwanda Government Ministry of Health where the MAH provided the product. Authorization in Rwanda was granted on 13 March 2023.

In July 2020, EMA granted marketing authorization for the 2-dose heterologous Ad26.ZEBOV, MVA-BN-Filo Ebola vaccine regimen under the trade names ZABDENO and MVABEA, respectively, although the products have not yet been administered in EU markets. An exemption to the sunset clause provisions was granted by the European Commission in February 2023. On 3 May 2021, a "Temporary Authorization for Use" was granted by the health authority of the DRC (la Direction de la Pharmacie et du Médicament) to deploy the Ad26.ZEBOV, MVA-BN-Filo vaccine in the DRC. Both vaccines received WHO prequalification in April 2021 and have been approved in Ghana (17 March 2022), Cote d'Ivoire (14 June 2022), Gabon (17 February 2023), Rwanda (13 March 2023), Sierra Leone (14 March 2023), Uganda (29 March 2023), and Nigeria (31 May 2023).

Postauthorization exposure data presented below have been retrieved from the UMURINZI/EBL4002 program (based on data provided by the Rwanda Ministry of Health) and the EBL4004 program.

SV.1.1. Method used to Calculate Exposure

Not applicable.

SV.1.2. Exposure

An estimated 243,161 and 214,211 participants in the post-approval vaccination campaigns UMURINZI/EBL4002 in Rwanda and EBL4004 in the DRC were exposed to Ad26.ZEBOV and MVA-BN-Filo, respectively, from approval to 26 September 2023.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Vaccines in general are not considered to present a risk for abuse potential, and this is also applicable to Ad26.ZEBOV and MVA-BN-Filo. The potential for misuse of Ad26.ZEBOV and MVA-BN-Filo is negligible given their composition, mechanism of action, and availability only through administration by medical personnel as a 2-dose vaccine regimen with or without a booster dose.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Risks not Included in the List of Safety Concerns in the RMP
Risks with minimal clinical impact on individuals (in relation to the severity of the indication):
Risk 1: Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation, or stress-related reactions (as a psychogenic response to the needle injection)
Risk 2: Nervous system disorders: headache*, dizziness postural*
Risk 3: Gastrointestinal disorders: vomiting, nausea*
Risk 4: Musculoskeletal and connective tissue disorders: myalgia, arthralgia
Risk 5: General disorders and administration site conditions: injection site pain, injection site pruritus, injection site swelling, injection site erythema, injection site warmth, injection site induration, fatigue, chills, decreased activity*, pyrexia
Risk 6: Metabolism and nutrition disorders: decreased appetite*
Risk 7: Psychiatric disorders: irritability*
Risk 8: Skin and subcutaneous tissue disorders: pruritus
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication:
Not applicable
Known risks that require no further characterization and are followed up via routine pharmacovigilance and for which the risk minimization messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorized):
Risk 1: Hypersensitivity reactions including anaphylaxis (see below for more information on anaphylaxis)
Known risks that do not impact the risk-benefit profile:
Not applicable

Risks not Included in the List of Safety Concerns in the RMP
Other reasons for considering the risks not important:
Risk 1: medication error (see below for more information on medication error)

***** Only reported as an adverse reaction following vaccination with Ad26.ZEBOV.

Anaphylaxis

Allergic reactions, possibly severe reactions (eg, hypersensitivity reactions and anaphylaxis), are known to occur with any injectable vaccine. Ad26.ZEBOV and MVA-BN-Filo contain ingredients with known potential to cause allergic reactions. To date, severe allergic reactions have not been identified as a safety issue in the data available for Ad26-based and MVA-based vaccines. No events of anaphylaxis were reported in the Ad26.ZEBOV, MVA-BN-Filo clinical trial safety pooling.

Anaphylaxis is not considered an important potential risk as it does not require further characterization by additional pharmacovigilance activities, or risk minimization beyond standard clinical practice. The routine risk minimization measures included in the Ad26.ZEBOV and MVA-BN-Filo SmPC and PL are part of standard clinical practice for vaccines in general and are considered sufficient for purposes of risk communication.

The SmPC Section 4.3 states that Ad26.ZEBOV and MVA-BN-Filo should not be used in individuals with hypersensitivity to the active substance or to any of their excipients, or to trace residues (chicken or egg protein and gentamicin) of MVA-BN-Filo. The SmPC Section 4.4 states that close observation is recommended following vaccination for the early signs of anaphylaxis or anaphylactoid reactions. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine. Individuals should be observed by a healthcare professional for at least 15 minutes after vaccination.

Medication Error

Insufficient immunogenicity of the vaccine(s) in case of ‘failure to vaccinate’ (due to medication error) leading to lack of anticipated clinical benefit is an expected undesirable clinical outcome (related to efficacy) arising from medication errors. Other potential undesirable clinical outcomes of medication errors are unknown. No safety concerns are expected from medication errors. Any AE arising as a consequence of a medication error will be monitored via routine pharmacovigilance and will be presented in each Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report.

More details on the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen, the related (possible) medication errors, and the risk minimization activities included in the product information are provided below.

The selected vaccine regimen

Various vaccine regimens based on Ad26 and MVA vectors, varying in vaccine dose level, monovalent or multivalent Ad26 vaccine, vaccine sequence, and dose interval were assessed for immunogenicity (and efficacy in nonhuman primates [NHP]).

The regimen selected for further clinical development was the Ad26.ZEBOV, MVA-BN-Filo sequence with a 56-day interval. This choice is primarily based on the fact that this regimen, at the selected vaccine dose levels (ie, $5x10^{10}$ vp for Ad26.ZEBOV and $1x10^{8}$ Inf.U for MVA-BN-Filo), provides protection to the otherwise lethal EBOV challenge in NHP. Clinical trial results confirmed the immunogenicity of the regimen in humans and showed that the 56-day interval is leading to a higher antibody response than shorter intervals.

Although the 2-dose vaccine regimen of Ad26.ZEBOV followed by MVA-BN-Filo with a 56-day interval was chosen as the recommended vaccine regimen, it was shown that all evaluated heterologous regimens induced robust humoral and cellular immune responses at 21 days post Dose 2, regardless of vaccine sequence, when an interval of at least 28 days between doses was respected.

Possible medication errors and clinical information relevant to dosing recommendations

Data supporting the corrective actions to be taken in the field in case the vaccine regimen was not administered as recommended, are discussed below.

The following situations are described:

- reverse vaccination sequence in the 8-week interval, ie, MVA-BN-Filo as Dose 1 and Ad26.ZEBOV as Dose 2;
- homologous regimens, ie, administration of the same vaccine twice;
- other intervals between the 2 vaccine doses in the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen;
- incomplete vaccination, ie, only 1 dose administered.

<u>Reverse vaccination sequence (MVA-BN-Filo as Dose 1 and Ad26.ZEBOV as Dose 2) in the 8-week interval</u>

Ad26.ZEBOV was selected to be given as the first vaccine in the Ad26.ZEBOV, MVA-BN-Filo 2-dose regimen. Phase 1 data provide evidence that, if MVA-BN-Filo is erroneously given as first vaccine, the reverse-order 2-dose regimen induces binding and neutralizing immune responses with the same order of magnitude at 21 days post Dose 2 and at later time points. This implies that revaccination with the correct sequence is not required if an MVA-BN-Filo, Ad26.ZEBOV regimen has been administered with an interval of approximately 8 weeks between doses.

Overall, no safety concerns were identified in adults using 2-dose heterologous vaccine regimens with reverse order. The MVA-BN-Filo, Ad26.ZEBOV vaccine regimen was well tolerated, and no

notable differences were observed in the overall occurrence and severity of solicited and unsolicited AEs between the reverse-order and selected-order vaccine regimens. In conclusion, no safety concerns are expected in case the vaccines would erroneously be administered in the reverse order.

In addition, Trial EBL1002 assessed the safety of an Ad26.ZEBOV booster dose given 1 year after the initial dose of the reverse-order regimen (14-, 28- and 56-day intervals) compared to after the selected-order regimen (28-day interval). There was no apparent influence of the administration of a booster dose given 1 year after the initial dose of the reverse-order vaccine regimen on the overall occurrence of AEs.

Homologous 2-dose regimens (Ad26.ZEBOV, Ad26.ZEBOV or MVA-BN-Filo, MVA-BN-Filo)

Homologous 2-dose regimens of both Ad26.ZEBOV and MVA-BN-Filo were assessed in Trial EBL1002. A homologous Ad26.ZEBOV, Ad26.ZEBOV regimen induced binding and neutralizing antibody responses, albeit of a smaller magnitude compared to the heterologous regimens. With a homologous MVA-BN-Filo, MVA-BN-Filo regimen, binding and neutralizing antibody responses were only weak or not quantifiable. In this trial, participants vaccinated with homologous regimens received a booster dose with the heterologous Ad26.ZEBOV or MVA-BN-Filo after which a strong anamnestic response was observed 7 days later, with binding and neutralizing antibody levels of similar magnitude compared to post-booster vaccination in people previously vaccinated with the heterologous Ad26.ZEBOV, MVA-BN-Filo regimen in a 28-day interval. These data, although limited, indicate that an erroneous homologous administration can be ‘corrected’ with a subsequent heterologous vaccination approximately 8 weeks after the last dose.

Overall, no safety concerns were identified in adults using 2-dose homologous vaccine regimens. Both homologous active vaccine regimens were well tolerated, and no notable differences were observed when comparing the overall occurrence and severity of solicited and unsolicited AEs between the homologous and heterologous regimens. In conclusion, no safety concerns are expected in case the same vaccine would erroneously be administered twice.

In addition, there was no apparent influence of the administration of a booster dose given 1 year after the initial dose of a homologous vaccine regimen on the overall occurrence of AEs.

Ad26.ZEBOV, MVA-BN-Filo regimen in intervals other than the 8-week interval (shorter and longer intervals)

During the course of the clinical development program, the 56-day interval was selected as most suitable, although both 28-day and 84-day intervals were also immunogenic.

Binding antibody concentrations measured at 21 days post Dose 2 tended to be lower with shorter intervals, especially in intervals shorter than 28 days. On the other hand, no obvious difference in the level of cellular immune responses was observed between the 28-day and the 56-day interval. Nonclinical data indicated 80% protection after vaccination in a 6-week interval and more variable percentages of survival rates in a 4-week interval.

Similar binding antibody responses at 21 days post Dose 2 were seen in the 84-day interval as in the 56-day interval. Moreover, for participants who received the second vaccine dose later than planned (ie, up to 483 days post Dose 1), binding antibody responses at least as high as in the 56-day interval were observed. Therefore, additional vaccine doses are not required in case of administration of the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen in intervals longer than 8 weeks.

Overall, no safety concerns were identified in adults, adolescents, and children after vaccination with the Ad26.ZEBOV, MVA-BN-Filo regimen at intervals ≥28 days (ie, 28, 56, or ≥84 days). All vaccination intervals were well tolerated, and there was no apparent influence of the time interval between the Ad26.ZEBOV and MVA-BN-Filo dose on the occurrence of solicited and unsolicited AEs. Similarly, no notable safety concerns were identified in adults after vaccination with the heterologous Ad26.ZEBOV, MVA-BN-Filo regimen in a 14-day interval compared with the 28-day interval. Also, different vaccine intervals with the reverse-order active vaccine regimen did not result in any safety issue.

In conclusion, no safety concerns were identified using 2-dose heterologous vaccine regimens with different vaccination intervals, hence no safety issues are expected in case the vaccines would erroneously be administered in a different interval than approximately 8 weeks.

Incomplete vaccination, ie, only 1 dose administered

If only 1 of the vaccines, either Ad26.ZEBOV or MVA-BN-Filo, is received, the efficacy is expected to be reduced as compared to the 2-dose vaccine regimen.

Limited EBOV GP-specific binding antibody data are available in follow-up of a single dose of Ad26.ZEBOV (based on results from Trial EBL2001 where a subset of participants was followed up to 6 months after single vaccination with Ad26.ZEBOV). After a single dose of Ad26.ZEBOV, EBOV GP-specific binding antibody responses were observed in all participants at all assessed time points, with stable antibody concentrations between 56 days and 6 months post Dose 1. These antibody concentrations were approximately 9- to 27-fold lower as compared to 21 days post Dose 2 in people vaccinated with the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen in a 56-day interval (EBL2001, EBL2002, EBL3001; subjects who received only Dose 1, as well as the available data prior to Dose 2 of subjects who received Dose 1 and 2).

Therefore, in case only 1 dose is received (either Ad26.ZEBOV or MVA-BN-Filo), it is recommended to complete the vaccine regimen with the heterologous vaccine in the recommended timeframe of 8 weeks or as soon as possible if 8 weeks have elapsed. If the second vaccination (MVA-BN-Filo) of the regimen has been delayed beyond the recommended 8 weeks after the first vaccination (Ad26.ZEBOV) of the regimen, the MVA-BN-Filo vaccine should be administered regardless of the elapsed time from the first vaccination with Ad26.ZEBOV.

No notable safety concerns were identified in case of incomplete vaccination.

Medication errors during the clinical development program

No safety issues were identified after vaccination with reversed order vaccines, homologous vaccines, or different vaccination intervals, which could be considered as medication errors, as summarized above.

No cases of overdose have been reported.

The following medication error was reported during the clinical development program and is considered relevant for situations that could occur in the field:

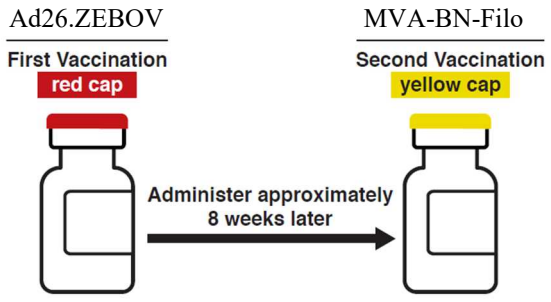
- One healthy participant received the vaccine regimen twice (at 2 different trial sites), ie, first in the 84-day interval schedule and second in the 28-day interval schedule. Dose 1 of the second regimen was received 8 days after Dose 2 of the first regimen. Adverse events were similar to those reported with the recommended vaccine regimen.

No notable safety issues were reported.

Risk minimization measures

The potential for medication error, including overdose, is minimized due to the product's design, detailed instructions on the posology and method of administration in the product information, and the administration taking place under the supervision of a healthcare professional. Further guidance and detailed information are included in the product information.

The vaccines should be administered by a trained healthcare worker. The vaccines are supplied in single-dose vials (0.5 mL) with vaccine-specific colored caps, allowing easy identification of the products. The SmPC Section 4.2 and PL Section 3 state that a dose (0.5 mL) of Ad26.ZEBOV (red cap vial) vaccine should be administered as the first vaccination and a dose (0.5 mL) of MVA-BN-Filo (yellow cap vial) vaccine should be administered as the second vaccination approximately 8 weeks after the first vaccination with Ad26.ZEBOV. In addition, a figure (see below) to visualize the vaccine regimen is included.



These instructions will minimize the risk of overdose, administration of an inverted or homologous vaccine regimen, vaccination with a different interval, or incomplete vaccination in the clinical

settings where the vaccine needs to be administered. SmPC Section 4.2 and PL Section 3 also provide instructions in case of inadvertent administration, which are described below:

- If MVA-BN-Filo is inadvertently administered as the first vaccination, administration of Ad26.ZEBOV is recommended as the second vaccination approximately 8 weeks later.

- If Ad26.ZEBOV is inadvertently administered as the first and the second vaccination, additional immunization with MVA-BN-Filo is recommended approximately 8 weeks after the second vaccination with Ad26.ZEBOV.

- If MVA-BN-Filo is inadvertently administered as the first and the second vaccination, additional immunization with Ad26.ZEBOV is recommended approximately 8 weeks after the second vaccination with MVA-BN-Filo.

- If the second vaccination (MVA-BN-Filo) of the regimen has been delayed beyond the recommended 8 weeks after the first vaccination (Ad26.ZEBOV) of the regimen, the MVA-BN-Filo vaccine should be administered regardless of the elapsed time from the first vaccination with Ad26.ZEBOV.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
Important identified risks	
None	
Important potential risks	
None	
Missing information	
Use during pregnancy	As being pregnant or planning to become pregnant was an exclusion criterion in all clinical trials conducted to date, the safety profile of Ad26.ZEBOV and MVA-BN-Filo in pregnant women has not been established and the risk in this population has not yet been defined. However, the morbidity and mortality risks to mother and fetus following EVD are very high, hence vaccination should not be withheld when there is a clear risk of exposure to Ebola infection.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Removal of the missing information 'Use during pregnancy'

There were no data from the use of Ad26.ZEBOV and MVA-BN-Filo in pregnant women at the time of the initial marketing authorization. Since then, data on use in pregnant women has been collected through the additional pharmacovigilance activity EBL3010, Trial EBL3008, and the

post-approval vaccination campaigns UMURINZI/EBL4002 and EBL4004.

The totality of the data from pregnant women vaccinated with the Ad26.ZEBOV, MVA-BN-Filo vaccination regimen demonstrated that the vaccine regimen was generally safe and well tolerated in the women and their infants. Data from Trial EBL3008 and the post-approval vaccination campaigns revealed no vaccine-associated congenital anomalies or feto/neonatal toxicity. In Trial EBL3010, the percentage of women with any adverse maternal/fetal or neonatal/infant outcome was similar in vaccinated pregnant women versus unvaccinated pregnant women. There was a numerical imbalance in cases of neonatal death, although the rates were below the background neonatal death rate.

Trial EBL3010 has been completed and a recommendation to preferably only use Ad26.ZEBOV and MVA-BN-Filo during pregnancy if the benefits of immediate vaccination outweigh the potential risks is included in Section 4.6 of the SmPC. There is no reasonable expectation that future feasible pharmacovigilance studies could further characterize the risk. Therefore, use during pregnancy is no longer considered missing information.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Important identified risks

None

Important potential risks

1. Thrombosis with thrombocytopenia syndrome

Missing Information:

None

MedDRA version 26.0 was used to classify the clinical trials adverse event (AE) information that is summarized in this section, unless specified otherwise. MedDRA terms used in the database search for each important risk are detailed in Annex 7.3.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Potential Risk: Thrombosis with thrombocytopenia syndrome

Potential Mechanisms:

TTS is a syndrome that was not reported as such before COVID-19 vaccine mass vaccinations began (ASH 2022). The syndrome is called vaccine-induced TTS when associated with vaccination (Huynh 2021). Several experts also consider that anti-platelet factor 4 (PF4) antibodies should be present to make a diagnosis of vaccine-induced TTS (Buoninfante 2022; Pavord 2021). TTS is characterized by thrombosis (frequently at unusual sites such as the cerebral venous

sinuses), mild to severe thrombocytopenia, elevated anti-PF4 antibodies and elevated D-dimer levels. Onset of symptoms is within 4 to 42 days after vaccination (ASH 2022).

Since the first appearance of vaccine-induced TTS in association with the Janssen and AstraZeneca COVID-19 vaccines, specific elements of the pathogenesis of vaccine-induced TTS started to be revealed by experts in the field. Although vaccine-induced TTS was shown to be associated with these 2 adenovirus vector-based COVID-19 vaccines, emerging evidence suggests that the cause of vaccine-induced TTS is multifactorial (ie, combination of adenovirus vector platform, SARS-CoV-2 Spike protein, and a potential role of a predisposition of the patient).

Nonclinical studies were performed with the Janssen COVID-19 vaccine (Ad26.COV2.S) to address several hypotheses for the pathogenesis of TTS including a potential role of the Ad26 vector. However, the available (mechanistic) nonclinical data generated do not permit a conclusion on the potential mechanism of TTS.

Evidence Source(s) and Strength of Evidence:

TTS, in some cases also accompanied by bleeding, has been observed very rarely following vaccination with the Janssen COVID-19 vaccine (Ad26.COV2.S), as well as with other COVID-19 adenovirus-vectored vaccines. As the mechanism of TTS is not understood, a potential contributory role for Ad26 vector cannot be excluded.

Characterization of the Risk:

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with Ad26.COV2.S. This includes severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcomes have been reported. These cases occurred within the first 3 weeks following vaccination, and mostly in individuals <60 years of age.

The cases were assessed by the Company using the case definition as requested by the PRAC, which is based on the case definition as proposed by the United Kingdom's National Institute for Health and Care Excellence (NICE) (NICE 2022) (Annex 7.4.1).

TTS Following Vaccination With Ad26.COV2.S

TTS is considered an important identified risk for Ad26.COV2.S. Cumulatively through 24 February 2023, Janssen has received 1 confirmed case of vaccine-associated TTS from clinical studies and a total of 360 cases of TTS from post marketing sources (including spontaneous and solicited cases). Of these cases, 353 were reported after the primary dose and 7 after the booster dose. Eighty of these cases were medically unconfirmed (all reported after the primary dose), all other cases were medically confirmed.

TTS in Other Non COVID-19 Ad26-based Vaccine Programs including Ad26.ZEBOV

Up to 26 September 2023, no cases of vaccine-associated TTS have been identified with non COVID-19 Ad26-based vaccines.

Risk Factors and Risk Groups:

As this is a potential risk no risk factors or risk groups can be identified.

Preventability:

The SmPC Section 4.4 states the theoretical risk of TTS and for healthcare professionals to be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia.

Impact on the Risk-Benefit Balance of the Product:

The occurrence of a vaccine-induced case of TTS could have an impact on the product's benefit risk profile, particularly if occurring in an otherwise healthy subject and/ or having a fatal outcome. Up to 26 September 2023, no cases of vaccine-induced TTS have been identified following vaccination with the Ad26.ZEBOV vaccine. As the underlying mechanism of action for vaccine-induced TTS associated with adenoviral vector-based COVID-19 vaccines is not fully elucidated, there is a theoretical concern for vaccine-induced TTS to occur after vaccination with the Ad26.ZEBOV vaccine. The current benefit offered by the vaccine outweighs the theoretical risk of TTS considering the severity and lethality of Ebola.

Public Health Impact:

No cases of vaccine-induced TTS have been identified following vaccination with the Ad26.ZEBOV vaccine. Therefore, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

PT Thrombosis with thrombocytopenia syndrome

SVII.3.2. Presentation of the Missing Information

Not applicable.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	Thrombosis with thrombocytopenia syndrome
Missing Information	None

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Follow-up Questionnaires for Safety Concerns	
Safety Concern	Purpose/Description
Not applicable	

Other Forms of Routine Pharmacovigilance Activities		
Activity	Objective/Description	Milestones
Cumulative reviews in the Periodic Benefit-Risk Evaluation Report (PBRER) / Periodic Safety Update Report (PSUR) of thromboembolic events, including potential TTS cases, following exposure to Ad26.ZEBOV	To further characterize the important potential risk of thrombosis with thrombocytopenia syndrome	Ongoing cumulative safety reviews presentation in PBRERs/PSURs.

III.2. Additional Pharmacovigilance Activities

Not Applicable

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing 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 authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Not applicable				

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy Studies which are conditions of the marketing authorizations				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Evaluation of a heterologous, two-dose preventive Ebola vaccine for field effectiveness. VAC52150EBL4006 Planned	To ensure adequate monitoring of effectiveness, the MAH will perform this study to collect data in the context of the intended use of the Ad26.ZEBOV, MVA-BN-Filo prophylactic vaccine regimen.	Clinical effectiveness	There are no prespecified milestones. The collection of clinical effectiveness data will depend on the occurrence and evolution of Ebola outbreaks.	Status to be reported annually within each annual reassessment application.

In the absence of efficacy data from clinical trials, the efficacy of the 2-dose primary vaccination regimen has been assessed through challenge studies in NHP, the most relevant animal model for EBOV disease. The 2-dose primary vaccination regimen administered at an interval of 8 weeks was protective down to a first dose of $2x10^9$ vp of Ad26.ZEBOV, in combination with $1x10^8$ Inf.U of MVA-BN-Filo, in a lethal intramuscular EBOV Kikwit NHP challenge model. Humoral immune responses, as measured by the level of EBOV GP-binding antibodies, were strongly correlated to survival in NHP.

The protective effect of the vaccine regimen in humans has been inferred from immunogenicity data (ie, comparison of EBOV GP-binding antibody concentrations). Data from 5 completed clinical trials (EBL2001, EBL2002, EBL3001, EBL3002, and EBL3003) conducted in Europe, the United States, and Africa in 764 adults (18-50 years of age) who had received the 2-dose primary vaccination regimen at the 8-week interval were used in this analysis. Anti-EBOV GP-binding antibodies were correlated with a protective effect against a rapidly progressing, fully lethal Ebola virus infection in NHP. The human immune responses measured 21 days post Dose 2 were associated with an increase of the predicted survival probability from 0% (ie, fully lethal) to 53.4% (98.68% CI: 33.8%; 70.9%) using the animal model. Based on this analysis, the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen can be anticipated to have a protective effect against EBOV disease in humans.

This vaccine regimen has been authorized under ‘exceptional circumstances’. This means that for scientific reasons, it has been impossible to obtain complete information on this vaccine regimen. The clinical development plan for the vaccine regimen includes a strategy for collecting effectiveness data when feasible.

In 2 previous EVD outbreaks, in addition to ring vaccination with the rVSV-ZEBOV-GP vaccine, the Strategic Advisory Board of Experts (SAGE) recommended vaccination of lower-risk

populations with the Ad26.ZEBOV, MVA-BN-Filo regimen under informed consent (SAGE 2019, WHO 2019e, WHO 2021c). In both circumstances, studies were designed to evaluate effectiveness, but both outbreaks were declared over before such an assessment could be made.

- Trial EBL3008 in DRC was designed to evaluate effectiveness during the 10th EVD outbreak in the DRC (outbreak ended 25 June 2020 [CDC 2020]).
- Trial EBL4005 in Guinea and Sierra Leone was designed to evaluate effectiveness during the EVD outbreak in Guinea (outbreak ended 19 June 2021 [CDC 2021b]).

The MAH will revise the EU-RMP as needed when data from Trial EBL4006 are available.

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Potential Risks	
Thrombosis with thrombocytopenia syndrome	**Routine risk communication:** • SmPC Section 4.4 • PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • SmPC Section 4.4, and PL Section 2 provide recommendations to address the theoretical risk of thrombosis with thrombocytopenia syndrome. **Other routine risk minimization measures beyond the Product Information:** • None

V.2. Additional Risk Minimization Measures

Not applicable.

V.2.1. Removal of Additional Risk Minimization Activities

Activity 1	Safety Concern(s) Addressed/Rationale for the Removal of Additional Risk Minimization Activity
Not applicable	

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks		
Thrombosis with thrombocytopenia syndrome	**Routine risk minimization measures:** • SmPC Section 4.4 • PL Section 2 **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:** • Cumulative reviews in the PBRER/PSUR of thromboembolic events, including potential TTS cases, following exposure to Ad26.ZEBOV **Additional pharmacovigilance activities:** • None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Ebola Vaccine (Ad26.ZEBOV [Recombinant, Replication-incompetent]) and Ebola Vaccine (MVA-BN-Filo [Recombinant, Non-replicating])

This is a summary of the risk management plan (RMP) for Ebola vaccine (Ad26.ZEBOV [recombinant, replication-incompetent]), further referred to as Ad26.ZEBOV, and Ebola vaccine (MVA-BN-Filo [recombinant, non-replicating]), further referred to as MVA-BN-Filo. The RMP details important risks of Ad26.ZEBOV and MVA-BN-Filo, how these risks can be minimized, and how more information will be obtained about Ad26.ZEBOV's and MVA-BN-Filo's risks and uncertainties (missing information).

Ad26.ZEBOV's and MVA-BN-Filo's Summary of Product Characteristics (SmPC) and their package leaflet (PL) give essential information to healthcare professionals and individuals on how Ad26.ZEBOV and MVA-BN-Filo should be used.

This summary of the RMP for Ad26.ZEBOV, MVA-BN-Filo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ad26.ZEBOV, MVA-BN-Filo's RMP.

I. The Vaccine and What it is Used For

Ad26.ZEBOV and MVA-BN-Filo, as part of the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen are authorized for active immunization for prevention of disease caused by Ebola virus (*Zaire ebolavirus* species) in individuals ≥1 year of age (see SmPC for the full indication). It contains Ad26.ZEBOV and MVA-BN-Filo as the active substances and it is given by intramuscular injection.

Further information about the evaluation of Ad26.ZEBOV's and MVA-BN-Filo's benefits can be found in Ad26.ZEBOV's and MVA-BN-Filo's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:

- https://www.ema.europa.eu/en/medicines/human/EPAR/zabdeno (for Ad26.ZEBOV)
- https://www.ema.europa.eu/en/medicines/human/EPAR/mvabea (for MVA-BN-Filo)

II. Risks Associated with the Vaccine and Activities to Minimize or Further Characterize the Risks

Important risks of Ad26.ZEBOV and MVA-BN-Filo, together with measures to minimize such risks and the proposed studies for learning more about Ad26.ZEBOV's and MVA-BN-Filo's risks, are outlined below.

Measures to minimize the risks identified for vaccines can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to individuals and healthcare professionals;
- Important advice on the vaccine's packaging;
- The authorized pack size — the amount of vaccine in a pack is chosen so to ensure that the vaccine is used correctly;
- The vaccine's legal status — the way a vaccine is supplied to the individual (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

Important risks of Ad26.ZEBOV and MVA-BN-Filo are risks that need special risk management activities to further investigate or minimize the risk, so that the vaccine can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ad26.ZEBOV and MVA-BN-Filo. Potential risks are concerns for which an association with the use of these vaccines is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the vaccines that is currently missing and needs to be collected (eg, on the long-term use of the vaccines).

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	Thrombosis with thrombocytopenia syndrome
Missing information	None

II.B. Summary of Important Risks

Important Potential Risk: Thrombosis with thrombocytopenia syndrome	
Evidence for linking the risk to the medicine	TTS, in some cases accompanied by bleeding, has been observed very rarely following vaccination with the Janssen COVID-19 vaccine (Ad26.COV2.S), as well as with other COVID-19 adenovirus-vectored vaccines. As the mechanism of TTS is not understood, a potential contributory role for Ad26 vector cannot be excluded.
Risk factors and risk groups	As this is a potential risk no risk factors or risk groups can be identified.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4 • PL Section 2 Additional risk minimization measure • None

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorization or specific obligation of Ad26.ZEBOV, MVA-BN-Filo:

VAC52150EBL4006: Evaluation of a heterologous, two-dose preventive Ebola vaccine for field effectiveness.

Purpose of the study: To ensure adequate monitoring of effectiveness, the MAH will perform this study to collect data in the context of the intended use of the Ad26.ZEBOV, MVA-BN-Filo prophylactic vaccine regimen.

II.C.2. Other Studies in Postauthorization Development Plan

There are no studies required for Ad26.ZEBOV and MVA-BN-Filo.

PART VII: ANNEXES

Table of Contents

Annex 4 Specific Adverse Drug Reaction Follow-up Forms

Annex 6 Details of Proposed Additional Risk Minimization Measures (if Applicable)

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6: Details of Proposed Additional Risk Minimization Activities (if Applicable)

Not applicable.