Janssen Vaccines & Prevention B.V. *

Clinical Protocol

A Phase 2 Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of a Heterologous 2-dose Vaccination Regimen Using Ad26.ZEBOV and MVA-BN®-Filo in Infants Aged 4-11 Months in Guinea and Sierra Leone

Protocol VAC52150EBL2005; Phase 2
AMENDMENT 4

Innovative Medicines Initiative-2
EBOVAC3 Consortium Partners
(London School of Hygiene and Tropical Medicine,
Institut National de la Santé et de la Recherche Médicale,
University of Antwerp,
College of Medicine and Allied Health Sciences,
and Janssen Vaccines & Prevention B.V.)

VAC52150 (Ad26.ZEBOV, MVA-BN-Filo [MVA-mBN226B])

*Janssen Vaccines & Prevention B.V. is a Janssen pharmaceutical company of Johnson & Johnson and is hereafter referred to as the sponsor of the study. The sponsor is identified on the Contact Information page that accompanies the protocol.

Status: Approved
Date: 28 September 2021
Prepared by: Janssen Vaccines & Prevention B.V.
EDMS number: EDMS-ERI-171651296, 15.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Date
Amendment 4	This document
Amendment 3	06 August 2020
Amendment 2	01 October 2019
Amendment 1	07 March 2019
Original Protocol	06 December 2018

Amendments below are listed beginning with the most recent amendment.

Amendment 4 (This document)
The overall reason for the amendment: The overall reason for the amendment is to offer participants enrolled in the control arm the possibility to receive the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen.

Rationale: Per the protocol amendment 3 dated 6 August 2020: "*Upon completion of the study, sites may offer the Ad26.ZEBOV, MVA BN Filo vaccine (if licensed and/or WHO prequalified) to the control arm upon consultation with the health authorities*." The current protocol Amendment 4 describes the extension of the study for participants originally enrolled in the control arm who consent to receiving the Ebola vaccine regimen. The extension phase will consist of a screening, vaccination, and safety follow-up phase until 28 days post-dose 2. The primary interim analysis for the blinded phase of the study will be done when all participants have completed the 12 months post-dose-1 visit or have left the main study (ie, completion of the main study), and the clinical database is locked and unblinded. This analysis will include all available data up to the 12 months post-dose-1 (D365) visit. Subsequently, participants who were originally randomized to the control arm and who have not withdrawn during the main study, will be offered the Ebola vaccine regimen in an optional extension phase of the study.
The final analysis will be performed at study completion, defined as the date of final database lock. This will occur after all participants have completed the last study-related visit or left the study.

14.4 Preparation, Handling, and Storage 16.1 Study-specific Design Considerations 16.2.3 Informed Consent 17.4 Subject Identification, Enrollment, and Screening Logs 17.9 Monitoring REFERENCES Appendix 1 Test of Understanding
Rationale: Few cases of convulsions/seizures (with or without observed fever) were reported following post-approval use of Ad26.ZEBOV in young children (1 to 17 years of age), for which a causal relation to vaccination is plausible.
1.3.3 Known Risks REFERENCES
Rationale: Provide information and guidance for investigators on signs and symptoms and on medical management should very rare events of thrombosis with thrombocytopenia syndrome (TTS) occur, as observed in another Ad26-based vaccine program (Ad26.COV2.S, COVID-19 vaccine). The Ad26.ZEBOV vaccine uses the same Ad26 vector as Ad26.COV2.S, but has different transgene inserts. To date, no cases of TTS have been reported in Janssen's Ad26.ZEBOV clinical studies nor in any other Ad26-based non-COVID-19 vaccine programs from Janssen. Nonetheless, TTS will be followed in this protocol as a serious adverse event that needs to be reported to the sponsor within 24 hours of awareness.
ABBREVIATIONS 1.3.4 Potential Risks 4.2.2 Exclusion Criteria 9.1.1 Overview 12.3.2.1 Thrombosis with Thrombocytopenia Syndrome REFERENCES Appendix 3: Thrombotic Events to be Reported
Rationale: The time intervals that should be respected between COVID-19 vaccination and study intervention were specified.
ABBREVIATIONS 4.3 Prohibitions and Restrictions 8 PRESTUDY AND CONCOMITANT THERAPY
Rationale: Clarified how study results may be made available to participants according to local standards/restrictions.
16.1 Study-specific Design Considerations
Rationale: Process for protocol clarification communications added to align with Janssen internal Standard Operation Procedures.
17.1 Protocol Clarification Communications
Rationale: A COVID-19 Appendix has been added to provide guidance to investigators for managing study-related procedures during the COVID-19 pandemic.
18 COVID-19 Appendix: Guidance on Study Conduct During the COVID-19 Pandemic
Rationale: Minor textual changes and corrections have been made.
Throughout the protocol.

Amendment 3 (06 August 2020)

The overall reason for the amendment: The overall reason for the amendment is to ensure that final analysis Clinical Study Report (CSR) is completed within 6 months of study completion, in line with European Medicines Agency (EMA) Article 46.

The changes made to the clinical protocol VAC52150EBL2005 in order to expedite the final analysis are listed below, including the rationale of each change and a list of all applicable sections.

Rationale: In order to expedite the final analysis, the interim analysis is being removed from the protocol. The final analysis will be performed at study completion, now defined as final database lock, which will occur after the last participant in the study has completed their last study-related visit, or left the study.

SYNOPSIS
3.1 Overview of Study Design

5 INTERVENTION ALLOCATION AND BLINDING

11 STATISTICAL METHODS
11.6 Interim Analysis
17.9.1 Study Completion/End of Study

Rationale: The statistical methods that will be used to analyze laboratory toxicities, vital sign abnormalities, and physical examination findings have been updated. Laboratory abnormalities will not be summarized since assessments are only performed at screening and pre-dose 2. A full physical examination is only conducted at screening. At other visits, only brief, symptom-directed examinations will be performed and clinically significant abnormal findings recorded as AEs. Therefore, separate analysis of physical examination findings will not be performed.

SYNOPSIS
11.4 Safety Analyses

Rationale: In line with the current protocol template, the Confidentiality Statement on the title page was updated and a footer was added.

Throughout the document

Amendment 2 (01 October 2019)

The overall reason for the amendment: This amendment is written in response to the questions received from FDA on 21 May 2019.

The changes made to the clinical protocol VAC52150EBL2005 are listed below, including the rationale of each change and a list of all applicable sections.

Rationale: The current criteria for local erythema and swelling adopted in the VAC52150EBL2005 protocol are less stringent than those used in the DMID pediatric toxicity table and ongoing Phase 2 and 3 studies in the Janssen clinical development program. The protocol will be amended to change the criteria for local erythema and swelling to be aligned with VAC52150EBL3001.

Local Erythema and Swelling	Grade 1	Grade 2	Grade 3	Grade 4
VAC52150EBL2005 (Current)	≥10 <25 mm	≥25 <50 mm	≥50 mm	Hospitalization or ER visit for treatment
VAC52150EBL2005 (Revised)	<10 mm	10 25 mm	26 50 mm	>50 mm or any grade 3 with hospitalization or ER visit for treatment

Appendix 2: Toxicity Grading Scale for Healthy Pediatric Participants up to 3 Years of Age Enrolled in Preventive Vaccine Clinical Trials

Rationale: The pausing rules were modified to include injection site ulceration, abscess, or necrosis occurring in 2 or more participants.

9.3.2 Study Pausing Rules

Rationale: Exclusion criterion 4 was modified to reflect allergy to MenACWY. The constituents of the Nimenrix vaccine were added to the exclusion criteria (*Neisseria meningitidis* polysaccharide, tetanus toxoid). The other listed ingredients (sucrose, trometamol, sodium chloride, water for injections) are not known to be associated with an allergic response.

4.2 Exclusion Criteria

Rationale: As axillary temperature will be measured, and this tends to underestimate the core temperature, the upper axillary temperature limit to allow vaccination was modified from ≥38.0°C to ≥37.5°C to prevent inadvertent vaccination of infants with low-grade fever.

1.3.5 Overall Benefit/Risk Assessment
4.2 Exclusion Criteria
6.1 Criteria for Postponement of Vaccination

Rationale: A typo in exclusion criterion 12 was corrected (platelet count <100 x 10^9/L instead of <100 x 10^{12}/L).

4.2 Exclusion Criteria

Rationale: Throughout the document, it was clarified that Physical Examination findings (ie, abnormalities) prior to Dose 1 vaccination are to be recorded as medical history and after Dose 1 as adverse event.

SYNOPSIS
Time and Events Schedule
9.3.1 Safety Assessments
11.4 Safety Analyses

Rationale: Information with regard to the number of times the parent(s)/guardians will be allowed to retake the test of understanding (TOU) was aligned across the protocol. They will be allowed to retake the test twice and have to achieve the passing score (≥90%) after the third time for their child to be eligible for the study.

16.1 Study-specific Design Considerations

Rationale: Question 9 of the TOU was adjusted to ask the participants if the clinical staff can share information about the participant's baby with other people **not** involved in the study instead of people involved in the study.

Appendix 1: Test of Understanding

Rationale: Minor editorial changes were made throughout the document.

Throughout the document

Amendment 1 (07 Mar 2019)

The overall reason for the amendment: The overall reason for the amendment is to allow flexibility in the amount of blood to be drawn for immunogenicity assessments and to clarify the intended study population age range.

The changes made to the clinical protocol VAC52150EBL2005 are listed below, including the rationale of each change and a list of all applicable sections.

Rationale: Two phlebotomy methods are acceptable practice for obtaining blood from infants; however, the blood volumes obtained for each method could be slightly different. This amendment allows the site flexibility in selecting the most appropriate method for their population and details the differences in blood volumes according to each method.

A total blood volume of 8.0-9.5 mL will be obtained: 2.0 mL for safety and 6.0-7.5 mL for immunogenicity depending on the most successful phlebotomy method, either the direct (vacutainer) method or indirect (syringe) method. If the indirect (syringe) method is chosen, the immunogenicity blood sample is 2.0 mL per visit and the total blood volume is 8 mL. If the direct (vacutainer) method is chosen, then the immunogenicity blood sample is 2.5 mL per visit and the total blood volume is 9.5 mL. The maximum amount of blood that will be drawn on a single visit will not exceed 3.5 mL.

SYNOPSIS
Time and Events Schedule
9.1.1 Overview
9.4 Immunogenicity Assessments
16.1 Study-specific Design Considerations

Rationale: The protocol was updated to clarify that the study population will include infants ≥4 months up to <12 months of age.

SYNOPSIS
1.4 Overall Rationale for the Study
3.1 Overview of Study Design
3.2 Study Design Rationale
4.1 Inclusion Criteria

SYNOPSIS

A Phase 2 Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of a Heterologous 2-dose Vaccination Regimen Using Ad26.ZEBOV and MVA-BN®-Filo in Infants Aged 4-11 Months in Guinea and Sierra Leone

Janssen Vaccines & Prevention B.V. (hereafter referred to as the sponsor), in collaboration with Bavarian Nordic GmbH (BN), and in conjunction with an Innovative Medicines Initiative (IMI) consortium led by the sponsor and the London School of Hygiene and Tropical Medicine (LSHTM), including the Institut National de la Santé et de la Recherche Médicale (INSERM), the University of Antwerp, and the College of Medicine and Allied Health Sciences (COMAHS) as partners, is investigating the potential of a prophylactic Ebola vaccine regimen (VAC52150) comprised of the following 2 candidate Ebola vaccines:

Ad26.ZEBOV is a monovalent vaccine expressing the full-length Ebola virus (EBOV, formerly known as *Zaire ebolavirus*) Mayinga glycoprotein (GP). The vaccine is produced in the human cell line PER.C6®.

MVA-mBN226B, further referred to as Modified Vaccinia Ankara (MVA)-BN®-Filo, is a multivalent vaccine expressing the EBOV GP, the Sudan virus (SUDV) GP, the Marburg virus (MARV) Musoke GP, and the Tai Forest virus (TAFV, formerly known as *Côte d'Ivoire ebolavirus*) nucleoprotein (NP). The EBOV GP expressed by MVA-BN-Filo has 100% homology to the one expressed by Ad26.ZEBOV.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Main Study

Objectives	Endpoints
Primary	
• To assess the safety and reactogenicity of a heterologous 2-dose vaccination regimen utilizing Ad26.ZEBOV (first vaccination; Dose 1) and MVA-BN-Filo (second vaccination; Dose 2) administered intramuscularly (IM) on Days 1 and 57, respectively.	• Solicited local and systemic adverse events until 7 days post-dose-1 and 7 days post-dose-2. • Unsolicited adverse events from the first vaccination until 28 days post-dose-1 and from the second vaccination until 28 days post-dose-2. • Any serious adverse events until 6 months post-dose-2, and serious adverse events related to study intervention until the end of the study.
Secondary	
• To assess binding antibody responses as measured by ELISA at 21 days post-dose-2.	• Binding antibody levels against the EBOV GP using FANG ELISA (EU/mL) at 21 days post-dose-2.
Exploratory	
• To assess binding antibody responses as measured by ELISA at baseline and 12 months post-dose-1.	• Binding antibody levels against the EBOV GP using FANG ELISA (EU/mL) at baseline and 12 months post-dose-1.

Objectives	Endpoints
• To assess the neutralizing antibody response to the adenovirus backbone as measured by the Ad26 virus neutralization assay (VNA) at baseline.	• Neutralizing antibody levels against the adenovirus backbone using Ad26 VNA at baseline.

ELISA: enzyme-linked immunosorbent assay; EU/mL: ELISA units/mL; FANG: Filovirus Animal Nonclinical Group.

Extension Phase

Objectives	Endpoints
Primary	
• To provide the heterologous 2-dose vaccination regimen (Ad26.ZEBOV on Day 1 and MVA-BN-Filo on Day 57) to participants in the control arm of the main study.	• Completion of the heterologous 2-dose vaccination regimen (Ad26.ZEBOV on Day 1 and MVA-BN-Filo on Day 57).
Exploratory	
• To assess the safety and reactogenicity of a heterologous 2-dose vaccination regimen utilizing Ad26.ZEBOV (first vaccination; Dose 1) and MVA-BN-Filo (second vaccination; Dose 2) administered intramuscularly (IM) on Days 1 and 57, respectively.	• Solicited local and systemic adverse events until 7 days post-dose-1 and 7 days post-dose-2. • Unsolicited adverse events from the first vaccination until 28 days post-dose-1 and from the second vaccination until 28 days post-dose-2. • Any serious adverse events until 28 days post-dose-2.

Hypothesis

No formal statistical hypothesis testing is planned.

OVERVIEW OF STUDY DESIGN

Main Study

Study VAC52150EBL2005 is a Phase 2, randomized, active-controlled, double-blind study to evaluate the safety, reactogenicity, and immunogenicity of Ad26.ZEBOV (first vaccination) at a dose of $5x10^{10}$ viral particles (vp) followed by MVA-BN-Filo (second vaccination) at a dose of $1x10^{8}$ infectious units (Inf U) administered 56 days later in healthy infants aged 4-11 months (ie, ≥4 months up to <12 months). This study will be conducted in Guinea and Sierra Leone.

A total number of 107 infants is targeted to be enrolled and randomized to study vaccine (Ad26.ZEBOV, MVA-BN-Filo) or active control in a blinded fashion. Approximately equal numbers of participants will be enrolled in each country. Within each country, there will be stratification by age group (ie, ≥4 to ≤8 months, and >8 to <12 months of age).

Participants in the control arm will receive the World Health Organization (WHO)-prequalified Meningococcal Group A, C, W135, and Y conjugate vaccine MenACWY as first vaccination on Day 1 and as second vaccination on Day 57. All study participants will be vaccinated with MenACWY at 6 months

post-dose-2 vaccination (ie, in their second year of life), in keeping with the recommended immunization regimen for this vaccine.

Enrollment of participants will start with vaccination of a sentinel cohort of 16 infants before exposing the remainder of the infants to the study intervention. An Independent Data Monitoring committee (IDMC) will be commissioned for this study.

Enrollment will be organized as follows:

- Eight sentinel participants will be randomized in a 1:1 ratio to receive study vaccine (Ad26.ZEBOV, MVA-BN-Filo) or active control. The study responsible physician and investigators will review the blinded 48-hour safety data from these 8 participants.
- In the absence of safety concerns, another 8 participants will be enrolled to complete the sentinel cohort until a total of 16 participants are randomized in a 1:1 ratio to study vaccine or active control. Study enrollment will be paused while the IDMC reviews available safety data for the first 7 days post-dose-1 of these 16 participants.
- Upon a favorable review of safety data up to 7 days post-dose-1 by the IDMC, the remainder of the participants will be randomly assigned to study vaccine or active control in a 5:2 ratio.

A similar procedure will be implemented for the second vaccination. When the last participant in the sentinel cohort completes the 7-days post-dose-2 safety visit, the IDMC will review all available data up to that point and will give recommendation for the continuation of the study in the remaining participants.

The blinded investigators, together with the sponsor's medical monitor, will be responsible for the safety monitoring of the study. If at least one pre-specified pausing rule is met, administration of study intervention will be paused and an IDMC meeting will be convened.

After each vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions, or longer if deemed necessary by the investigator. Following the first and second vaccination, any unsolicited, solicited local or systemic adverse events, and vital signs will be documented by study-site personnel at the end of this observation period. In addition, solicited events will be recorded in a diary for 7 days post-dose-1 and post-dose-2.

Unsolicited adverse events will be recorded from the first vaccination onwards until 28 days post-dose-1, and again from the second vaccination until 28 days post-dose-2. Serious adverse events and/or special reporting situations that are related to study procedures or related to non-investigational (concomitant) sponsor products will be reported from the time a signed and dated informed consent form (ICF) is obtained onwards until the end of the study. All other serious adverse events and/or special reporting situations will be reported from the day of the first vaccination onwards until 6 months post-dose-2.

Safety assessments include solicited local or systemic adverse events, unsolicited adverse events, serious adverse events, physical examinations (including body length and weight), vital sign measurements, and laboratory assessments (blood samples will be collected at screening and at Day 57 pre-dose-2).

Blood samples will be collected for immunogenicity assessments at screening (ie, the baseline sample), 21 days post-dose-2, and 12 months post-dose-1.

The study will consist of a screening period of up to 28 days, a vaccination period in which the participants will be vaccinated at baseline (Day 1; first vaccination) followed by a second vaccination on Day 57, a vaccination with MenACWY at 6 months post-dose-2, and a follow-up period until 12 months post-dose-1.

Extension Phase

After the last participant has completed the 12 months post-dose-1 visit or has left the main study (ie, completion of the main study), there will be an interim database lock and unblinding of the study. Subsequently, participants who were originally randomized to the control arm and who have not withdrawn during the main study, will be offered the Ebola vaccine regimen in an optional extension phase of the study. Participants opting to receive the vaccine regimen will be followed-up for safety until 28 days post-dose-2. The IDMC will be replaced by an independent medical reviewer.

The study is considered completed at final database lock, which will occur after the last participant has completed the last study visit or left the study.

STUDY POPULATION

The study population will consist of healthy infants, aged 4-11 months (ie, ≥4 months up to <12 months) at screening for the main study (ie, blinded phase), who have received all routine immunizations appropriate for their age, and who have normal hemoglobin, platelet and white blood cell counts at screening. Participants who have received a candidate Ebola vaccine, or a candidate Ad26- or MVA-based vaccine in the past, or with known allergy or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine products, including known allergy to egg, egg products, and aminoglycosides, will be excluded.

DOSAGE AND ADMINISTRATION

Infants randomized to the Ad26.ZEBOV, MVA-BN-Filo arm will receive the following study vaccines as a 0.5-mL IM injection into the anterolateral thigh:

- Ad26.ZEBOV: $5x10^{10}$ vp on Day 1
- MVA-BN-Filo: $1x10^{8}$ Inf U on Day 57

Participants in the control arm will receive the WHO-prequalified MenACWY as first vaccination on Day 1 and as second vaccination on Day 57.

The recommended immunization series of MenACWY consists of 2 doses given 2 months apart, followed by a booster vaccination at 12 months of age. Previously unvaccinated children may receive a single dose in their second year of life. In keeping with the recommended immunization regimen for this vaccine, all participants will receive a dose of MenACWY at the 6-months post-dose-2 visit. The MenACWY vaccine will be administered as a 0.5-mL IM injection into the anterolateral thigh.

Upon completion of the main study, participants in the extension phase who were originally randomized to the control arm will receive the same vaccine regimen as the participants in the Ad26.ZEBOV, MVA-BN-Filo arm of the main study.

SAFETY EVALUATIONS

Brief physical examinations (including body length and weight) and vital signs will be assessed as indicated in the Time and Events Schedule. The investigators, together with the sponsor's medical monitor, will be responsible for the safety monitoring of the study, and will halt vaccination of further participants in case any of the pre-specified pausing rules have been met. An IDMC will be established to monitor data on an

ongoing basis to ensure the continuing safety of the participants enrolled in this study. In the extension phase, participants will be followed for safety until 28 days post-dose-2.

IMMUNOGENICITY EVALUATIONS

In the main study, blood samples (2.0-2.5 mL) for immunogenicity assessments will be collected at screening (ie, the baseline sample), 21 days post-dose-2 and 12 months post-dose-1. During the extension phase, no blood samples for immunogenicity evaluations will be collected.

STATISTICAL METHODS

The primary interim analysis for the blinded phase of the study will be done when all participants have completed the 12 months post-dose-1 visit or have left the main study (ie, completion of the main study), and the clinical database is locked and unblinded. This analysis will include all available data up to the 12 months post-dose-1 (D365) visit.

The final analysis will be performed at study completion, defined as the date of final database lock. This will occur after all participants have completed the last study-related visit or left the study. Specific details will be provided in the Statistical Analysis Plan.

No formal hypothesis will be tested.

Safety data will be analyzed descriptively (including 95% confidence intervals, if applicable) for participants receiving study vaccine or active control. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention arm. Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue study intervention due to an adverse event, or who experience a severe or a serious adverse event. Clinically significant abnormal laboratory data reported in the CRF will be presented in the data listings. Clinically significant vital sign abnormalities and abnormal findings of physical examinations will be recorded as AEs.

Descriptive statistics (geometric mean and 95% confidence interval, or median and range Q1-Q3, as appropriate) will be calculated for continuous immunologic parameters at all available time points. Graphical representations of immunological parameters will be made as applicable. Frequency tabulations will be calculated for discrete (qualitative) immunologic parameters as applicable.

TIME AND EVENTS SCHEDULE

Main Study

Study Procedures	Screening (≤28 days)[a]	Study Vaccination Period									Follow-up
		D1	D2-D7	D8 +1d	D29 ±7d	D57 ±7d	D58-D63	D64 +1d	D78 ±7d	D237 ±30d	D365 ±30d
		Dose 1		+7d pd1	+28d pd1	Dose 2		+7d pd2	+21d pd2	+6m pd2	+12m pd1
Screening/Administrative											
Test of Understanding (TOU)[b]	X										
Informed consent[c]	X										
Inclusion/exclusion criteria[d]	X	X									
Medical history and demographics	X										
Prestudy therapies[e]	X										
Randomization		X									
Vaccine Administration[d]		▲				▼				♦[f]	
Safety Assessments											
Brief physical examination[g]	X	X[h]		X		X[h]		X	X	X[h]	
Vital signs[i]	X	X[j]				X[j]				X[j]	
Distribution of participant diary		X				X					
Completion of diary at home[k]		X	X	X[h]		X	X	X[h]			
Review of diary by study-site personnel				X				X			
30 minutes post-vaccination observation[l]		X[l]				X[l]				X[f]	
Solicited adverse events recording[m]		X	X	X		X	X	X			
Unsolicited adverse events recording		From first vaccination (Day 1) onwards until 28 days post-dose-1				From second vaccination (Day 57) onwards until 28 days post-dose-2					
Serious adverse events[n]	Continuous until 6 months post-dose-2										X
Concomitant therapies[o]	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments											
Full blood count (1.0 mL)	X					X[h]					
Immunogenicity Assessments											
Blood sampling (serum) for assessment of immune responses (2.0–2.5 mL)	X[p]								X		X

	Screening (≤28 days)[a]	Study Vaccination Period									Follow-up
		D1	D2-D7	D8 +1d	D29 ±7d	D57 ±7d	D58-D63	D64 +1d	D78 ±7d	D237 ±30d	D365 ±30d
Study Procedures		**Dose 1**		+7d pd1	+28d pd1	**Dose 2**		+7d pd2	+21d pd2	+6m pd2	+12m pd1
Approximate blood draw volumes											
Safety: 1.0 mL	1.0					1.0					
Immunogenicity: 2.0-2.5 mL	2.0-2.5								2.0-2.5		2.0-2.5
Cumulative total (maximum)	**3.5**					**4.5**			**7.0**		**9.5[q]**

▲ *Ad26.ZEBOV 5x10^{10} vp or active control vaccine (MenACWY)* ▼ *MVA BN Filo 1x10^{8} Inf U or active control vaccine (MenACWY)* ♦ *MenACWY*
d: days; m: months; pd1: post dose 1; pd2: post dose 2

NOTE: If a participant did not receive study intervention on the planned day of vaccination, the timings of the next visits post vaccination will be determined relative to the actual day of vaccination.

NOTE: In case of early withdrawal due to an adverse event, the investigator or clinical designee will collect all information relevant to the adverse event and safety of the participant, and will follow the participant until resolution of the adverse event or until reaching a clinically stable endpoint. Participants who wish to withdraw consent (decided by the parent/guardian) will be offered an optional visit for safety follow up (before the formal withdrawal of consent). The parent(s)/guardian have the right to refuse such a visit for their child.

a. Screening may be split into multiple days or visits. Retesting of values (eg, safety laboratory) that lead to exclusion is allowed once using an unscheduled visit during the screening period, provided there is an alternative explanation for the out of range value. The safety laboratory assessments at screening are to be performed within 28 days prior to the first vaccination (including Day 1 before vaccination) and may be repeated if they fall outside this time window. If retesting is required, all screening procedures (except TOU) should be repeated.
b. The TOU should be administered to the parent or guardian who will provide consent, and will be administered after reading but before signing the informed consent form (ICF).
c. Signing of the ICF needs to be done before the first study-related activity (except TOU).
d. The investigators should ensure that all study enrollment criteria have been met at the end of the screening period and before the first vaccination on Day 1. If a participant's clinical status changes (including available laboratory results or the receipt of additional medical records) after screening but before Day 1 such that the participant no longer meets all eligibility criteria, then the participant will be excluded from participation in the study. For contraindications to receive the second vaccination, refer to Section 6.2.
e. Prestudy therapies administered up to 30 days prior to the start of screening and previous vaccinia/smallpox vaccination at any time prior to study entry must be recorded in the case report form (CRF) at screening.
f. MenACWY will be administered to all participants. After vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions, or longer if deemed necessary by the investigator. Participant diaries will not be distributed. Infants that experience any symptoms will be invited to come for an unscheduled visit as needed.
g. The brief physical examination (symptom-directed) includes also body length and weight. Physical examination findings (ie, abnormalities) prior to Dose 1 vaccination are to be recorded as medical history, after Dose 1 vaccination as adverse event.
h. Prior to study intervention administration.

i. Includes pulse/heart rate (at rest), respiratory rate, and body temperature.
j. Prior to study intervention administration and at the end of the observation period.
k. Diaries will be completed at home by either a project field worker who will visit the participant during daily visits or by the parent(s)/guardian to document symptoms of solicited local and systemic adverse events in the evening after each vaccination and then daily for the next 7 days at approximately the same time each day.
l. After the first and second vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions, or longer if deemed necessary by the investigator. Solicited local and systemic and unsolicited adverse events emerging during the observation period will be recorded in the CRF.
m. Solicited adverse events will be documented in the evening after the first and second vaccination and then daily for the next 7 days, during daily home visits by a project field worker.
n. Serious adverse events and/or special reporting situations that are related to study procedures or that are related to non-investigational (concomitant) sponsor products will be reported from the time a signed and dated ICF is obtained onwards until the end of the study. All other serious adverse events and/or special reporting situations will be reported from the day of the first vaccination onwards until 6 months post-dose-2.
o. Concomitant therapies must be recorded from screening onwards until 28 days post-dose-1 and from the second vaccination until 28 days post-dose-2. At the other time points, it should only be recorded if given in conjunction with serious adverse events.
p. This will serve as the baseline sample for immunogenicity assessments.
q. A total blood volume of 8.0-9.5 mL will be obtained: 2.0 mL for safety and 6.0-7.5 mL for immunogenicity depending on the most successful phlebotomy method, either the direct (vacutainer) method or indirect (syringe) method. If the indirect (syringe) method is chosen, the immunogenicity blood sample is 2.0 mL per visit and the total blood volume is 8 mL. If the direct (vacutainer) method is chosen, then the immunogenicity blood sample is 2.5 mL per visit and the total blood volume is 9.5 mL. Whenever feasible, a single phlebotomy method will be used for a given subject.

Study Extension for Vaccinating Participants From the Control Arm

	eScreening (≤28 days)[a]	Study Vaccination Period							
		eD1	eD2-eD7	eD8 +1d	eD29 ±7d	eD57 ±7d	eD58-eD63	eD64 +1d	eD85 ±7d
Study Procedures		**Dose 1**		+7d pd1	+28d pd1	**Dose 2**		+7d pd2	+28d pd2
Screening/Administrative									
Test of Understanding (TOU)[b]	X								
Informed consent[c]	X								
Inclusion/exclusion criteria[d]	X	X							
Vaccine Administration[d]		▲				▼			
Safety Assessments									
Brief physical examination[e]	X	X[f]		X		X[f]		X	X
Vital signs[g]	X	X[h]				X[h]			
Distribution of participant diary		X				X			
Completion of diary at home[i]		X	X	X[f]		X	X	X[f]	
Review of diary by study-site personnel				X				X	
30 minutes post-vaccination observation[j]		X[j]				X[j]			
Solicited adverse events recording[k]		X	X	X		X	X	X	
Unsolicited adverse events recording		From first vaccination (eDay 1) onwards until 28 days post-dose-1				From second vaccination (eDay 57) onwards until 28 days post-dose-2			
Serious adverse events[l]	X	Continuous until 28 days post-dose-2							
Concomitant therapies[m]	X	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments									
Full blood count (1.0 mL)	X					X[f]			

▲ *Ad26.ZEBOV $5x10^{10}$ vp*▼ *MVA BN Filo $1x10^{8}$ Inf U*

d: days; m: months; pd1: post dose 1; pd2: post dose 2; eDx: study extension Day x

NOTE: If a participant did not receive study intervention on the planned day of vaccination, the timings of the next visits post vaccination will be determined relative to the actual day of vaccination.

NOTE: In case of early withdrawal due to an adverse event, the investigator or clinical designee will collect all information relevant to the adverse event and safety of the participant, and will follow the participant until resolution of the adverse event or until reaching a clinically stable endpoint. Participants who wish to withdraw consent (decided by the parent/guardian) will be offered an optional visit for safety follow up (before the formal withdrawal of consent). The parent(s)/guardian have the right to refuse such a visit for their child.

a. Screening may be split into multiple days or visits. Retesting of values (eg, safety laboratory) that lead to exclusion is allowed once using an unscheduled visit during the screening period, provided there is an alternative explanation for the out of range value. The safety laboratory assessments at screening are to be performed within 28 days prior to the first vaccination (including Day 1 before vaccination) and may be repeated if they fall outside this time window. If retesting is required, all screening procedures (except TOU) should be repeated.
b. The TOU should be administered to the parent or guardian who will provide consent, and will be administered after reading but before signing the informed consent form (ICF).
c. Signing of the ICF for participation in the study extension needs to be done before the first study-related activity in the study extension (except TOU).
d. The investigators should ensure that all study enrollment criteria have been met at the end of the screening period and before the first vaccination on Day 1 of the study extension. If a participant's clinical status changes (including available laboratory results or the receipt of additional medical records) after screening but before Day 1 of the study extension such that the participant no longer meets all eligibility criteria, then the participant will be excluded from participation in the extension. For contraindications to receive the second vaccination in the study extension, refer to Section 6.2.
e. The brief physical examination (symptom-directed) includes also body length and weight. Physical examination findings (ie, abnormalities) after Dose 1 vaccination are to be recorded as adverse event.
f. Prior to study intervention administration.
g. Includes pulse/heart rate (at rest), respiratory rate, and body temperature.
h. Prior to study intervention administration and at the end of the observation period.
i. Diaries will be completed at home by either a project field worker who will visit the participant during daily visits or by the parent(s)/guardian to document symptoms of solicited local and systemic adverse events in the evening after each vaccination and then daily for the next 7 days at approximately the same time each day.
j. After the first and second vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions, or longer if deemed necessary by the investigator. Solicited local and systemic and unsolicited adverse events emerging during the observation period will be recorded in the CRF.
k. Solicited adverse events will be documented in the evening after the first and second vaccination and then daily for the next 7 days, during daily home visits by a project field worker.
l. Serious adverse events and/or special reporting situations that are related to study procedures or that are related to non-investigational (concomitant) sponsor products will be reported from the time a signed and dated ICF is obtained onwards until the end of the study. All other serious adverse events and/or special reporting situations will be reported from the day of the first vaccination onwards until 28 days post-dose-2. At the screening visit participants will also be asked about serious adverse events that occurred between the D365 follow-up visit of the main phase and the start of the extension phase. These will be recorded on the AE form.
m. Concomitant therapies must be recorded from screening onwards until 28 days post-dose-1 and from the second vaccination until 28 days post-dose-2. At the other time points, it should only be recorded if given in conjunction with serious adverse events.

ABBREVIATIONS

Adxx	adenovirus serotype xx (vector)
Ad26.ZEBOV	adenovirus serotype 26 expressing the Ebola virus Mayinga glycoprotein
AE	adverse event
BN	Bavarian Nordic GmbH
CI	confidence interval
COMAHS	College of Medicine and Allied Health Sciences
CRF	case report form
DMID	Division of Microbiology and Infectious Diseases
EBOV	Ebola virus
eDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
eD*x*	extension Day *x*
ELISA	enzyme-linked immunosorbent assay
EPI	Expanded Program on Immunization
EU	European Union
EUA	Emergency Use Authorization
EUL	Emergency Use Listing
EU/mL	ELISA units per mL
EVD	Ebola virus disease
FANG	Filovirus Animal Nonclinical Group
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	glycoprotein
HITT	heparin-induced thrombocytopenia and thrombosis
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (previously International Council for Harmonisation)
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IM	intramuscular(ly)
IMI	Innovative Medicines Initiative
Inf U	infectious units
INSERM	Institut National de la Santé et de la Recherche Médicale
IRB	Institutional Review Board
IWRS	interactive web response system
kb	kilobase
LSHTM	London School of Hygiene and Tropical Medicine
MARV	Marburg virus
MedDRA	Medical Dictionary for Regulatory Activities
MVA	Modified Vaccinia Ankara
MVA-BN-Filo	Modified Vaccinia Ankara Bavarian Nordic vector expressing multiple filovirus proteins
NHP	nonhuman primate(s)
NP	nucleoprotein
PCR	polymerase chain reaction
PREVAC	Partnership for Research on Ebola Vaccination
PQC	Product Quality Complaint
RBC	red blood cell
RNA	ribonucleic acid
SAP	Statistical Analysis Plan
SUDV	Sudan virus
SUSAR	suspected unexpected serious adverse reaction
TAFV	Tai Forest virus
THAM	tris (hydroxymethyl)-amino methane
TOU	Test of Understanding

TTS	thrombosis with thrombocytopenia syndrome
VISP	vaccine induced seropositivity
vp	viral particles
WBC	white blood cell
WHO	World Health Organization

DEFINITIONS OF TERMS

Study intervention	Ad26.ZEBOV, MVA-BN-Filo, or active control (MenACWY)
Independent study intervention monitor	An unblinded study intervention monitor assigned to the study who is responsible for the unblinded interface between the sponsor and the investigational site pharmacy.
Solicited adverse events (reactogenicity)	Local and systemic adverse events that are common and known to occur after vaccination and that are usually collected in a standard, systematic format in vaccine clinical studies. For the list of solicited adverse events in this study, see Section 9.3. For the purpose of vaccine clinical studies, all other adverse events are considered unsolicited; however, this definition should be distinguished from definitions based on pharmacovigilance guidelines.

Study Naming Convention

Clinical studies with the Ad26.ZEBOV and MVA-BN-Filo vaccines are referred to as study VAC52150EBLXXXX (eg, study VAC52150EBL1001), but also the abbreviation EBLXXXX (eg, study EBL1001) is used in this document.

1. INTRODUCTION

Janssen Vaccines & Prevention B.V. (hereafter referred to as the sponsor), in collaboration with Bavarian Nordic GmbH (BN), and in conjunction with an Innovative Medicines Initiative (IMI) consortium led by the sponsor and the London School of Hygiene and Tropical Medicine (LSHTM), including the Institut National de la Santé et de la Recherche Médicale (INSERM), the University of Antwerp, and the College of Medicine and Allied Health Sciences (COMAHS) as partners, is investigating the potential of a prophylactic Ebola vaccine regimen (VAC52150) comprised of the following 2 candidate Ebola vaccines:

Ad26.ZEBOV is a monovalent vaccine expressing the full-length Ebola virus (EBOV, formerly known as *Zaire ebolavirus*) Mayinga glycoprotein (GP). The vaccine is produced in the human cell line PER.C6®.

MVA-mBN226B, further referred to as Modified Vaccinia Ankara (MVA)-BN®-Filo, is a multivalent vaccine expressing the EBOV GP, the Sudan virus (SUDV) GP, the Marburg virus (MARV) Musoke GP, and the Tai Forest virus (TAFV, formerly known as *Côte d'Ivoire ebolavirus*) nucleoprotein (NP). The EBOV GP expressed by MVA-BN-Filo has 100% homology to the one expressed by Ad26.ZEBOV.

The monovalent vaccine is part of an ongoing development program for a multivalent vaccine against multiple filoviruses that cause disease in humans, including EBOV, SUDV, and MARV. For the most up-to-date nonclinical and clinical information regarding Ad26.ZEBOV and MVA-BN-Filo, refer to the latest versions of the Investigator's Brochures and Addenda (if applicable).[12,13,14,15,16] A brief summary of the nonclinical and clinical information available at the time of the protocol writing is provided below.

The term "study intervention" throughout the protocol, refers to study vaccine (Ad26.ZEBOV, MVA-BN-Filo)/active control.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "study" refers to the main double blinded part of the study. The current protocol describes the main study unless clearly specified otherwise.

1.1. Background

Ebola viruses belong to the Filoviridae family and cause Ebola virus disease (EVD), which can induce severe hemorrhagic fever in humans and nonhuman primates (NHP). Case fatality rates in EVD range from 25% to 90% (average: 50%), according to the World Health Organization (WHO).[22] These viruses are highly prioritized by the United States Government, who has defined them as 'Category A' agents, due to the high mortality rate of infected individuals. At the time of protocol writing, no licensed vaccine, treatment or cure existed for this disease.

Filoviruses are named for their long, filamentous shape. Within this filamentous virus, a single 19-kilobase (kb) negative-sense ribonucleic acid (RNA) genome encodes 7 proteins: the GP, the

polymerase, the NP, the secondary matrix protein, the transcriptional activator, the polymerase cofactor, and the matrix protein. The virion surface is covered by homotrimers of the viral GP, which is believed to be the sole host attachment factor for filoviruses. Following cell entry, the viruses replicate their genomes and viral proteins in the cytoplasm using an RNA-dependent RNA polymerase, which is carried into the cell together with the virus.[10]

In this Phase 2 study, the sponsor's adenovirus serotype 26 (Ad26) vector expressing the EBOV Mayinga GP (Ad26.ZEBOV) and the MVA-BN vector with EBOV, SUDV, and MARV GP inserts and TAFV NP insert (MVA-BN-Filo) will be evaluated as a heterologous 2-dose regimen, in which one vaccine (Ad26.ZEBOV) is used to prime a filovirus-specific immune response and the other vaccine (MVA-BN-Filo) is used to boost the immune response 56 days later. The EBOV GP that circulated in West Africa during the 2013-2016 epidemic had 97% homology to the EBOV GP used in this vaccine regimen.[3]

Clinical studies

The safety, reactogenicity, and immunogenicity of the Ad26.ZEBOV and MVA-BN-Filo vaccines are being evaluated in a number of completed and ongoing clinical studies in adults and children ≥1 year of age. The sponsor's current clinical development plan contains 4 completed Phase 1 studies (EBL1001, EBL1002, EBL1003, EBL1004), the ongoing Phase 1 studies EBL1005 and EBL1007, 4 ongoing Phase 2 studies (EBL2001, EBL2002, EBL2003, and EBL2004/Partnership for Research on Ebola Vaccination [PREVAC]), and 5 ongoing/planned Phase 3 studies (EBL3001, EBL3002, EBL3003, EBL3004, and EBL4001). Monovalent Ad26.ZEBOV vaccine and multivalent MVA-BN-Filo vaccine are combined in homologous or heterologous 2-dose regimens in which each vector is used to prime a filovirus-specific immune response followed by a second immunization with the same or the other vector at 7-, 14-, 28-, 56-, or 84-day intervals. An additional Phase 1 study with the multivalent vaccine VAC69120FLV1001 has been completed, where a group receiving Ad26.ZEBOV, MVA-BN-Filo in a 56-day interval was included as a control arm.

As of 19 October 2018 (ie, at the time of protocol writing), an estimated 6,500 participants (adults, children, HIV+ adults; estimation based on randomization ratios) have received at least the first vaccination (Ad26.ZEBOV, MVA-BN-Filo, or placebo/active comparator). Of these, approximately 1,600 children (1-17 years of age) and 400 HIV+ adults have been vaccinated.

Refer to the latest versions of the Ad26.ZEBOV and MVA-BN-Filo Investigator's Brochures and Addenda (if applicable) for more details.[12,13,14,15,16] A summary is provided below.

Phase 1 studies

Final analysis data are available for the 4 randomized, placebo-controlled, observer-blind, Phase 1 studies that were conducted in healthy adult Western (United Kingdom and United States) and African (Kenya, Tanzania, and Uganda) male and female participants, aged ≥18 to ≤50 years, outside of EBOV outbreak areas. In these studies, Ad26.ZEBOV and MVA-BN-Filo were administered intramuscularly (IM) as homologous or heterologous 2-dose regimens, in 7-, 14-, 28-, or 56-day intervals.

Both vaccines are well tolerated, with no safety concerns identified. Reactogenicity was slightly more commonly reported among participants following Ad26.ZEBOV than following MVA-BN-Filo vaccination. The most frequently reported solicited adverse events reported in the 4 individual Phase 1 studies were injection site pain, injection site warmth, fatigue, headache, and myalgia. The most frequently reported unsolicited adverse events were hypokalemia, neutropenia, and neutrophil count decreased.

The Ad26.ZEBOV, MVA-BN-Filo vaccine regimens are highly immunogenic and induce considerable humoral as well as cellular immune responses, regardless of vaccine sequence and dose level.

Phase 2/3 Studies

In the ongoing Phase 2 and 3 studies, enrollment of both adults and children is complete. Safety data from studies EBL2001 (United Kingdom, France), EBL2002 (Kenya, Uganda, Burkina Faso, Côte D'Ivoire), EBL3001 (Sierra Leone), EBL3002 (United States), and EBL3003 (United States) have been partially unblinded to group level in all participants in the Phase 2 and 3 studies for whom clean data up to the 6-months post-dose-2 visit are available. For participants who either have not completed the 6-months post-dose-2 visit or whose data are not considered clean, blinded group safety data is described below. The serious adverse event databases have been reconciled and include, in addition to the studies listed below, serious adverse event data from EBL2004 (PREVAC).

In general, the vaccination regimen of Ad26.ZEBOV followed by MVA-BN-Filo 56 days later was well tolerated and no safety signals were identified. The majority of solicited adverse events were of mild or moderate intensity after vaccination with Ad26.ZEBOV or MVA-BN-Filo. The frequency of grade 3 pyrexia (≥39.0°C) was less than 1% following vaccination and the incidence of any febrile response was less than 7.0% in any group. As expected, the frequency of local and systemic reactogenicity was more common in healthy adult participants who received active vaccine compared to placebo and was similar to the incidence reported in the Phase 1 studies. Reactogenicity was also slightly more commonly reported among participants following Ad26.ZEBOV than following MVA-BN-Filo vaccination which was also noted in the Phase 1 studies.

A review of the unblinded safety summary reveals that serious adverse events were reported in 46 healthy adults (2.2%) vaccinated with the active vaccine regimen and in 9 participants (2.2%) vaccinated with placebo. There was only one serious adverse event reported in HIV+ adults which occurred in the active vaccine group. From the still blinded studies, a total of 35 serious adverse events have been reported in adults, adolescents and children in study EBL2004 (PREVAC) of which approximately 23 may have been randomized to active vaccine based on the randomization schedule. One suspected unexpected serious adverse reaction (SUSAR) of small fiber neuropathy was reported following administration of Ad26.ZEBOV and 1 SUSAR of generalized pruritus was reported following administration of MVA-BN-Filo. There are no adverse drug reactions or events of special concern listed in the Investigator's Brochures.

Safety data in pediatric participants

Data on pediatric participants aged 1-3, 4-11, and 12-17 years from studies EBL2002 and EBL3001 are provided in a blinded manner (Table 1).

Table 1: Frequency of Solicited and Unsolicited Adverse Events in Children and Adolescents From Studies EBL2002 and EBL3001 – Blinded Data

	Adolescents (12-17 years of age)		Children (4-11 years of age)		Young children (1-3 years of age)	
	N=323[a]		N=324[a]		N=192[b]	
	n	%	n	%	n	%
Any solicited AEs	189	58.5	197	60.8	85	44.3
Any solicited grade 3 AEs	7	2.2	3	0.9	3	1.6
Any solicited local AEs	115	35.6	129	39.8	31	16.1
Any solicited local grade 3 AEs	2	0.6	3	0.9	0	0.0
Any solicited systemic AEs	164	50.8	139	42.9	68	35.4
Any solicited systemic grade 3 AEs	5	1.5	1	0.3	3	1.6
Injection site pain	105	32.5	114	35.2	30	15.6
Headache	127	39.3	65[c]	33.9	-	-
Fatigue	83	25.7	31[c]	16.1	-	-
Any pyrexia (defined as ≥38°C)	16	5.0	41	12.7	35	18.2
Grade 3 pyrexia (defined as ≥39°C)	4	1.2	0	0.0	2	1.0
Any unsolicited AEs	190	58.8	187	57.7	156	81.3
Any unsolicited grade 3 AEs	33	10.2	3	0.9	14	7.3
Serious adverse events	2	0.6	7	2.2	10	5.2
Serious adverse events within 28 days post any vaccination	0	0.0	0	0.0	8	4.2

AE: adverse event

Note: Data are from ongoing studies EBL2002 and EBL3001 with a snapshot data cut-off date of 25 September 2018 (EBL2002) and 19 September 2018 (EBL3001). These are data that were available at the time of protocol writing.

a) Based on studies EBL2002 and EBL3001.

b) Based on study EBL3001.

c) This was not a solicited AE in the 4 to 11-year-olds in EBL2002. Therefore, the denominator is based solely on EBL3001 (N=192).

The majority of the pediatric participants experienced at least 1 solicited adverse event post-vaccination (regimen). Approximately a third of the pediatric participants experienced at least 1 solicited local adverse event post-vaccination, with 5 participants reporting at least 1 grade 3 event. The most frequent solicited local adverse event was injection site pain. Solicited systemic adverse events were also common in any age group, with 9 participants reporting at least 1 grade 3 event. Headache and fatigue were the most frequent systemic adverse events among adolescents. Irritability/fussiness/crying/screaming, reduced activity/somnolence/fatigue and loss of appetite were common among children (4-11 years). Pyrexia (defined as ≥38°C) was reported in 5.0% of the adolescents, 12.7% of the children (4-11 years) and 18.2% of the young children (1-3 years). Four adolescents and 2 young children (1-3 years) reported a grade 3 pyrexia (defined as ≥39°C). Unsolicited adverse events were reported in the majority of adolescents and children with approximately equal incidence. Thirty-three adolescents and 3 children reported at least 1 grade 3

unsolicited adverse event. Infections/infestations were the most frequently reported classes of unsolicited adverse events.

There was 1 serious adverse event in Cohort 2b of study EBL2002: a 12-year-old male participant developed fever from malaria on Day 80 (post-dose-2 follow-up phase) and died 3 days later. This event was considered not related to the study vaccination.

In the Phase 3 study EBL3001, 192 children aged 1-3 years were randomized to receive the active vaccine or placebo. The blinded data available at the time of protocol writing, have revealed no major safety concerns thus far.

1.2. Active Comparator Vaccine

MenACWY

Participants in the control arm will receive the WHO-prequalified Meningococcal Group A, C, W135, and Y conjugate vaccine MenACWY as first vaccination on Day 1 and as second vaccination on Day 57. All study participants will be vaccinated with MenACWY at 6 months post-dose-2 (ie, in their second year of life), in keeping with the recommended immunization regimen for this vaccine.

1.3. Benefit/Risk Section

1.3.1. Known Benefits

Ad26.ZEBOV and MVA-BN-Filo

The clinical benefit of 2-dose combinations of Ad26.ZEBOV and MVA-BN-Filo is to be established.

MenACWY

To offer clinical benefit to participants in the control arm, an active vaccine MenACWY was chosen instead of placebo. Even when meningitis is diagnosed early and adequate treatment is started, 5% to 10% of patients die, typically within 24 to 48 hours after the onset of symptoms. Left untreated, up to 50% of cases may die. Bacterial meningitis may also result in brain damage, hearing loss or a learning disability in 10% to 20% of survivors.[23,24]

MenACWY is a WHO-prequalified vaccine indicated for active immunization of persons at risk of exposure to *Neisseria meningitidis* serogroups A, C, W135 and Y, to prevent invasive disease.

1.3.2. Potential Benefits

Ad26.ZEBOV and MVA-BN-Filo

Participants may benefit from clinical testing and physical examination; others may benefit from the knowledge that they may aid in the development of an Ebola vaccine. There is no direct individual benefit from vaccination for the participants at the current development stage.

1.3.3. Known Risks

Ad26.ZEBOV and MVA-BN-Filo

The safety, reactogenicity, and immunogenicity of the Ad26.ZEBOV and MVA-BN-Filo vaccines are being evaluated in a number of completed and ongoing clinical studies in adults and children ≥1 year of age. In these clinical studies, both vaccines are well tolerated, with no safety concerns identified. The vaccines mainly elicited some solicited local and systemic reactions, as expected with injectable vaccines, and no serious safety concerns in study participants. At the time of protocol writing, MVA-BN-based vaccines have been administered to more than 8,100 individuals without unexpected or serious adverse reactions reported. For details, see the safety data presented in Section 1.1.

Based on data from post-approval use in pediatrics (1 to 17 years of age) febrile seizure was identified as a rare adverse reaction in this population. Few cases of convulsions/seizures (with or without observed fever) were reported following post-approval use of Ad26.ZEBOV in young children, for which a causal relation to vaccination is plausible.[15]

In general, febrile seizures are prevalent, occurring in up to 5% of children, with the overall incidence estimated to be 460/100,000 in the age group of 0 4 years with peak incidence in the second year of life.[17] There may be developmental reasons for this observation since about 98-99% of children who experience febrile seizures recover without any sequelae or recurrence. Because the occurrence of febrile seizures (even without vaccination) is fairly common, the Brighton Collaboration has stressed that generalized convulsive seizure that follows administration of a vaccine may be temporally associated with, but is not necessarily the result of, administration of a vaccine.[4]

MenACWY

Very common side effects (affecting ≥1 in 10 people) of MenACWY vaccination include pain, erythema and swelling at the injection site, headache, feeling tired, irritable or sleepy, feeling generally unwell, and loss of appetite. For further information on the side effects of the administered vaccine by patient age group, refer to the most recent versions of the applicable vaccine prescribing information.

1.3.4. Potential Risks

The following potential risks will be monitored during the study and are specified in the protocol:

Risks Related to Vaccination

In general, IM injection may cause local itching, warmth, pain, tenderness, erythema, swelling, arm discomfort or bruising of the skin at vaccine injection sites.

Participants may exhibit general signs and symptoms associated with administration of a vaccine, including fever, chills, rash, nausea/vomiting, general itching, loss of appetite, diarrhea, decreased activity/lethargy, irritability/crying. These side effects will be monitored, but are generally short-term and do not require treatment.

Participants may have an allergic reaction to the vaccination. An allergic reaction may cause a rash, hives or even anaphylaxis. Severe reactions are rare. Medications must be available in the clinic to treat serious allergic reactions.

Risks from Blood Draws

As with all clinical studies requiring blood sampling, there are risks associated with venipuncture and multiple blood sample collection. Blood drawing may cause pain, tenderness, bruising, bleeding, dizziness, vaso-vagal response, syncope, and, rarely, infection at the site where the blood is taken. The total blood volume to be collected is considered to be an acceptable amount of blood over this time period from the population in this study (see Section 16.1).

Concomitant Vaccination

Concomitant vaccination might have an influence on both safety profile and immunogenicity of Ad26.ZEBOV and MVA-BN-Filo. Likewise, the study intervention might have an influence on both safety profile and immunogenicity of any concomitant vaccination. Therefore, a participant should not receive a live-attenuated vaccine from 30 days before the first vaccination until 30 days after the second vaccination unless a vaccine preventable disease such as measles emerges which would warrant administration of live-attenuated vaccines. Immunizations with inactivated vaccines should be administered at least 15 days before or after administration of any study intervention in order to avoid any potential interference in efficacy of the routine immunizations or the interpretation of immune responses to study intervention, as well as to avoid potential confusion with regard to attribution of adverse reactions. However, if a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study intervention. Otherwise, a participant will not postpone, forego or delay the receipt of any recommended vaccine according to local schedules (eg, Expanded Program on Immunization [EPI] schedule according to the WHO regional office for West Africa).

Note: National Immunization Plans will be available on site and these will be taken into consideration when planning vaccination schedules. Vaccination cards will be checked before administration of study intervention.

Vaccine Induced Seropositivity

The potential of a participant becoming PCR-positive after vaccination was assessed in study EBL1002. The risk for false positives is low and expected to decrease rapidly over time after administration of Ad26.ZEBOV, MVA-BN-Filo.

In general, uninfected participants in Ebola vaccine studies may develop Ebola-specific antibodies as a result of an immune response to the candidate Ebola vaccine, referred to as vaccine induced seropositivity (VISP). These antibodies may be detected in Ebola serologic tests, causing the test to appear positive even in the absence of actual Ebola infection. VISP may become evident during the study, or after the study has been completed.

Unknown Risks

There may be other risks that are not known. If any significant new risks are identified, the principal investigator and participants (parents/guardian) will be informed.

Thrombosis in combination with thrombocytopenia (thrombosis with thrombocytopenia syndrome [TTS]), has been observed following vaccination with the Janssen COVID-19 (Ad26.COV2.S) vaccine. As of 31 August 2021, there have been 2 to 3.1 cases reported per 1 Million adults who were vaccinated with the Janssen COVID-19 vaccine. Reports include severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis and arterial thrombosis, in combination with thrombocytopenia. The associated symptoms began typically within 4 weeks after vaccination or sometimes later. These events occurred mostly in women under 60 years of age, but have also been observed in men and in individuals older than 60 years of age. Cases of thrombosis in combination with thrombocytopenia have been fatal in some cases. The exact pathophysiology of TTS is unclear. This event has not been observed to date with any other Janssen Ad26-based vaccines (including with Ad26.ZEBOV), although TTS has been reported following vaccination with another COVID-19 vaccine based on modified adenovirus (the Astra-Zeneca COVID vaccine). Participants should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg pain or swelling, persistent abdominal pain, severe or persistent headaches, blurred vision or other vision changes, mental status changes or seizures (fits), skin bruising or petechiae beyond the site of vaccination or easy bleeding.

1.3.5. Overall Benefit/Risk Assessment

Based on the available data and proposed safety measures, the overall benefit/risk assessment for this clinical study is considered acceptable for the following reasons:

- To date, safety data from the studies in the clinical development program revealed no significant safety issues (see Section 1.1). Further experience from Ad26.ZEBOV or MVA-BN-Filo will be gained from currently ongoing clinical studies.
- For all participants, there are pre-specified pausing rules that would result in pausing of further vaccination if predefined conditions occur, preventing exposure of new participants to study intervention until an Independent Data Monitoring Committee (IDMC - main study) or an independent medical reviewer (extension phase) reviews all safety data (see Sections 3.1, 9.3.2 and11.7).
- Only participants who meet all inclusion criteria and none of the exclusion criteria (specified in Section 4) will be allowed to participate in this study (main study and extension phase). The selection criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study.
- Several safety measures are included in this protocol to minimize the potential risk to participants, including the following:
  - Vaccination in the main study will start with a sentinel cohort of 16 participants before exposing the remainder of the infants to the study intervention. See details in Section 3.1.

- Participants will remain at the site for at least 30 minutes after each vaccination to monitor the development of any acute reactions, or longer if deemed necessary by the investigator (eg, in case of grade 3 adverse events). Refer to Section 6 for more information on emergency care.
- Safety evaluations (physical examinations and vital sign measurements) will be performed at scheduled visits during the study, as indicated in the Time and Events Schedule.
- The investigator or clinical designee will document unsolicited adverse events from the first vaccination (Day 1) onwards until 28 days post-dose-1, and again from the second vaccination (Day 57) onwards until 28 days post-dose-2. The investigator or clinical designee will document serious adverse events and/or special reporting situations that are related to study procedures or that are related to non-investigational (concomitant) sponsor products from the time a signed and dated informed consent form (ICF) is obtained onwards until the end of the study. All other serious adverse events and/or special reporting situations will be reported from the day of the first vaccination onwards until 6 months post-dose-2 for the main study, and until 28 days post-dose-2 for the extension phase.
- Any clinically significant abnormalities (including those persisting at the end of the study/early withdrawal) will be followed by the investigator until resolution or until a clinically stable endpoint is reached.
- Participants will discontinue study intervention for the reasons included in Section 10.2.
- If acute illness (excluding minor illnesses such as diarrhea or mild upper respiratory tract infection) or axillary temperature ≥37.5°C occur at the scheduled time for vaccination, the participant may be vaccinated up to 10 days beyond the window allowed for the scheduled vaccination, or be withdrawn from that vaccination at the discretion of the investigator and after consultation with the sponsor (see Section 6.1).
- Contraindications to the second vaccination and MenACWY vaccination at 6 months post-dose-2 are included in Section 6.2.

1.4. Overall Rationale for the Study

This Phase 2 study aims to improve preparedness for future Ebola outbreaks by vaccination of a new, at-risk population. This study will be conducted in healthy infants aged 4-11 months (ie, ≥4 months up to <12 months) (referred to as 'infants') in Guinea and Sierra Leone. This study will expand the safety, reactogenicity, and immunogenicity database for VAC52150 to infants vaccinated with a heterologous 2-dose regimen with Ad26.ZEBOV followed by MVA-BN-Filo administered 56 days later.

This study will build on earlier studies with the candidate Ebola vaccines in older children aged 1 to 17 years (EBL2002: 4-11 and 12-17 years; EBL3001: 1-3, 4-11, and 12-17 years). Though the incidence of EVD in younger children is low, it has been reported that the mean incubation period (the average time from infection until symptom onset) in children was shortest on average in the youngest children, with means ranging from 6.9 days (95% confidence interval [CI], 5.1-9.5) in 14 children younger than 1 year of age, to 9.8 days (95% CI, 8.7-11.1) in 184 children

10-15 years of age. Younger children also had shorter times from symptom onset to hospitalization and from symptom onset to death, and the highest mortality rate.[1,20] It is therefore important to evaluate any vaccine for Ebola for safety and immunogenicity in this population.

A study extension phase has been instituted to provide control arm participants who were enrolled in the main study the opportunity to receive the Ebola vaccine regimen.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

Main Study

Objectives	Endpoints
Primary	
• To assess the safety and reactogenicity of a heterologous 2-dose regimen utilizing Ad26.ZEBOV (first vaccination; Dose 1) and MVA-BN-Filo (second vaccination; Dose 2) administered IM on Days 1 and 57, respectively.	• Solicited local and systemic adverse events until 7 days post-dose-1 and 7 days post-dose-2. • Unsolicited adverse events from the first vaccination until 28 days post-dose-1 and from the second vaccination until 28 days post-dose-2. • Any serious adverse events until 6 months post-dose-2, and serious adverse events related to study intervention until end of the study.
Secondary	
• To assess binding antibody responses as measured by ELISA at 21 days post-dose-2.	• Binding antibody levels against the EBOV GP using FANG ELISA (EU/mL) at 21 days post-dose-2.
Exploratory	
• To assess binding antibody responses as measured by ELISA at baseline and 12 months post-dose-1.	• Binding antibody levels against the EBOV GP using FANG ELISA (EU/mL) at baseline and 12 months post-dose-1.
• To assess the neutralizing antibody response to the adenovirus backbone as measured by Ad26 virus neutralization assay (VNA) at baseline.	• Neutralizing antibody levels against the adenovirus backbone using Ad26 VNA at baseline.

ELISA: enzyme-linked immunosorbent assay, EU/mL: ELISA units/mL; FANG: Filovirus Animal Nonclinical Group.

Extension Phase

Objectives	Endpoints
Primary	
• To provide the heterologous 2-dose vaccination regimen (Ad26.ZEBOV on Day 1 and MVA-BN-Filo on Day 57) to participants in the control arm of the main study.	• Completion of the heterologous 2-dose vaccination regimen (Ad26.ZEBOV on Day 1 and MVA-BN-Filo on Day 57).

Objectives	Endpoints
Exploratory	
• To assess the safety and reactogenicity of a heterologous 2-dose vaccination regimen utilizing Ad26.ZEBOV (first vaccination; Dose 1) and MVA-BN-Filo (second vaccination; Dose 2) administered intramuscularly (IM) on Days 1 and 57, respectively.	• Solicited local and systemic adverse events until 7 days post-dose-1 and 7 days post-dose-2. • Unsolicited adverse events from the first vaccination until 28 days post-dose-1 and from the second vaccination until 28 days post-dose-2. • Any serious adverse events until 28 days post-dose-2.

Refer to Section 9 for evaluations related to endpoints.

2.2. Hypothesis

No formal statistical hypothesis testing is planned.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

3.1.1. Main Study

This is a Phase 2, randomized, active-controlled, double-blind study to evaluate the safety, reactogenicity, and immunogenicity of Ad26.ZEBOV (first vaccination) at a dose of $5x10^{10}$ viral particles (vp) followed by MVA-BN-Filo (second vaccination) at a dose of $1x10^{8}$ infectious units (Inf U) administered 56 days later in healthy infants aged 4-11 months (ie, ≥4 months up to <12 months). This study will be conducted in Guinea and Sierra Leone.

A total number of 107 infants is targeted to be enrolled and randomized to study vaccine (Ad26.ZEBOV, MVA-BN-Filo) or active control in a blinded fashion. Approximately equal numbers of participants will be enrolled in each country. Within each country, there will be stratification by age group (ie, ≥4 to ≤8 months, and >8 to <12 months of age).

Participants in the control arm will receive the WHO-prequalified Meningococcal Group A, C, W135, and Y conjugate vaccine MenACWY as first vaccination on Day 1 and as second vaccination on Day 57. All study participants will be vaccinated with MenACWY at 6 months post-dose-2 (ie, in their second year of life), in keeping with the recommended immunization regimen for this vaccine.

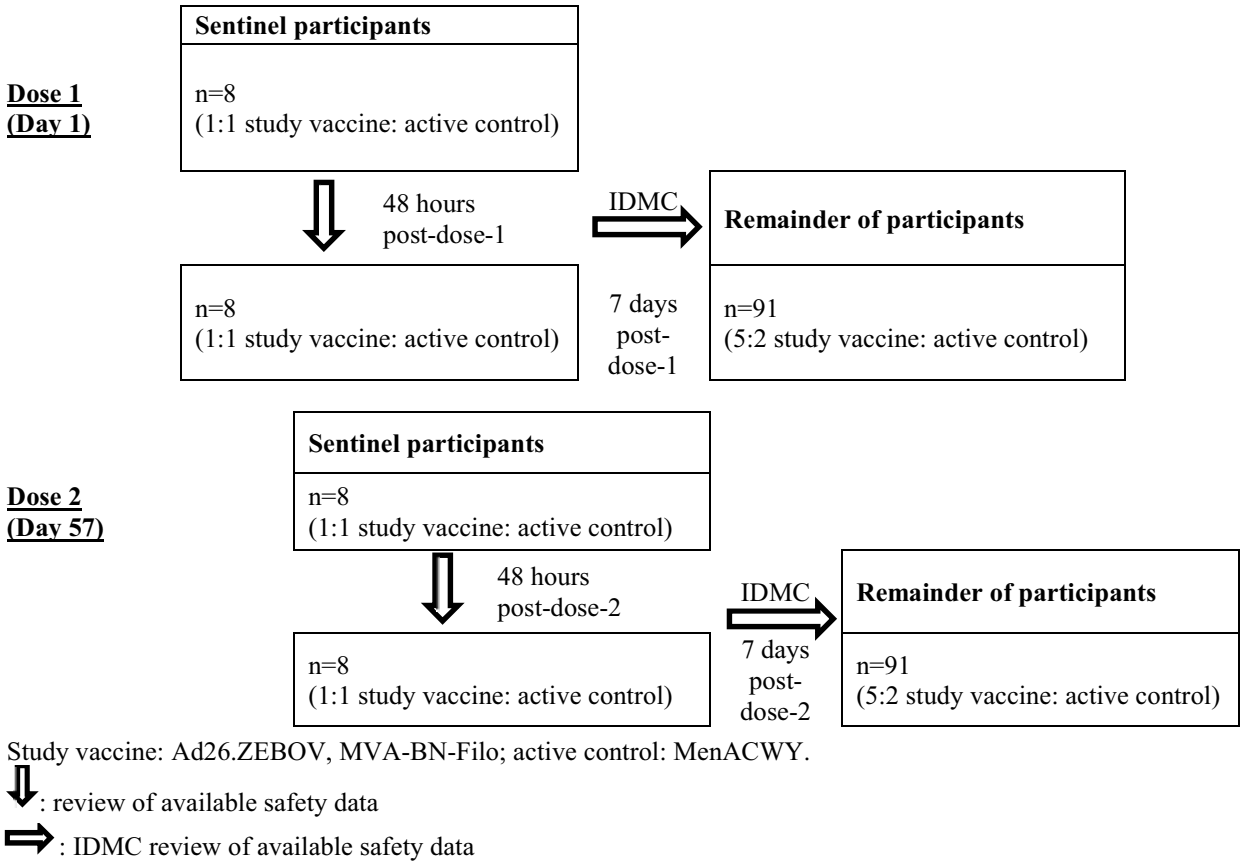
Enrollment of participants will start with vaccination of a sentinel cohort of 16 infants before exposing the remainder of the infants to the study intervention. An IDMC will be commissioned for this study. Refer to Section 11.7 for details.

Enrollment will be organized as follows:

- Eight sentinel participants will be randomized in a 1:1 ratio to receive study vaccine (Ad26.ZEBOV, MVA-BN-Filo) or active control. The study responsible physician and investigators will review the blinded 48-hour safety data from these 8 participants.
- In the absence of safety concerns, another 8 participants will be enrolled to complete the sentinel cohort until a total of 16 participants are randomized in a 1:1 ratio to study vaccine or active control. Study enrollment will be paused while the IDMC reviews available safety data for the first 7 days post-dose-1 of these 16 participants.
- Upon a favorable review of safety data up to 7 days post-dose-1 by the IDMC, the remainder of the participants will be randomly assigned to study vaccine or active control in a 5:2 ratio.

A similar procedure will be implemented for the second vaccination (see Figure 1). When the last participant in the sentinel cohort completes the 7-days post-dose-2 safety visit, the IDMC will review all available data up to that point and will give recommendation for the continuation of the study in the remaining participants.

Figure 1: Schematic Overview of the Main Study



Study vaccine: Ad26.ZEBOV, MVA-BN-Filo; active control: MenACWY.

⇩: review of available safety data

⇨: IDMC review of available safety data

The blinded investigators, together with the sponsor's medical monitor, will be responsible for the safety monitoring of the study. If at least one pre-specified pausing rule is met, administration of study intervention will be paused and an IDMC meeting will be convened (see Section 9.3.2).

After each vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions, or longer if deemed necessary by the investigator. Following the first and second vaccination, any unsolicited, solicited local or systemic adverse events, and vital signs will be documented by study-site personnel at the end of this observation period.

The participant's parent/guardian will be given a thermometer, ruler and participant diary with instructions for the proper recording of events occurring after the first and second vaccination. Diaries will be completed at home by either a project field worker who will visit the participant or by the parent(s)/guardian to document solicited local (at injection site) and systemic adverse events and body temperature, beginning on the evening of the first and second vaccination, and then daily for the next 7 days. Temperatures should be taken at approximately the same time each day, preferably in the evening and additionally whenever the child feels warm. Study-site personnel will collect and review participant diary information at the 7-day post-vaccination visit (first and second vaccination).

Unsolicited adverse events will be recorded from the first vaccination (Day 1) onwards until 28 days post-dose-1, and again from the first vaccination (Day 57) onwards until 28 days post-dose-2. Serious adverse events and/or special reporting situations that are related to study procedures or are related to non-investigational (concomitant) sponsor products will be reported from the time a signed and dated ICF is obtained onwards until the end of the study. All other serious adverse events and/or special reporting situations will be reported from the day of the first vaccination onwards until 6 months post-dose-2.

Safety assessments include solicited local or systemic adverse events, unsolicited adverse events, serious adverse events, physical examinations (including body length and weight), vital sign measurements, and laboratory assessments (blood samples will be collected at screening and at Day 57 pre-dose-2).

Blood samples will be collected for immunogenicity assessments at screening (ie, the baseline sample), 21 days post-dose-2, and 12 months post-dose-1.

The study will consist of a screening period of up to 28 days, a vaccination period in which the participants will be vaccinated at baseline (Day 1; first vaccination) followed by a second vaccination on Day 57, a vaccination with MenACWY at 6 months post-dose-2, and a post-dose-2 follow-up until 12 months post-dose-1.

The main study is considered completed after the last participant has completed the 12 months post-dose-1 visit or has left the main study and the study has been unblinded.

3.1.2. Extension Phase

After the last participant has completed the 12 months post-dose-1 visit or has left the main study (ie, completion of the main study), there will be an interim database lock and unblinding of the study. Subsequently, participants who were originally randomized to the control arm and who have not withdrawn during the main study, will be offered the Ebola vaccine regimen in an optional extension phase of the study. Participants opting to receive the vaccine regimen will be followed-up for safety until 28 days post-dose-2. The IDMC will be replaced by an independent medical reviewer. No immunogenicity assessments will be performed in the extension phase.

3.2. Study Design Rationale

This study is designed to obtain information on the safety, reactogenicity and immunogenicity in infants aged 4-11 months (ie, ≥4 months up to <12 months), in order to be prepared for a future Ebola outbreak. Infants younger than 4 months of age are not included to avoid interference with routine immunization schedules.

The measures taken in this study ensure the safety of this population. A full blood count will be performed at screening because there is a high prevalence of anemia in this population. In the Phase 3 study EBL3001, 192 children aged 1-3 years old were randomized to receive the active vaccine or placebo. The blinded data available at the time of protocol writing, have revealed no major safety concerns thus far.

Blinding and Control

An active control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Randomization will be used to minimize bias in the assignment of participants to intervention arms, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention arms, and to enhance the validity of statistical comparisons across intervention arms. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

The extension phase for participants enrolled in the control arm will be open label.

4. PARTICIPANT POPULATION

4.1. Main Study

Screening for eligible participants will be performed within 28 days before administration of the study intervention.

The inclusion and exclusion criteria for enrolling participants in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

4.1.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Parent(s) (preferably both if available or as per local requirements)/guardian must sign an ICF indicating that he or she understands the purpose of, and procedures required for the study, and potential risks and benefits of the study, and are willing to allow their child to participate in the study.
2. Parent(s)/guardian are willing/able to ensure that their child adheres to the prohibitions and restrictions specified in this protocol (see Section 4.3).
3. The parent(s)/guardian must be at or above the age of legal consent in the jurisdiction in which the study is taking place.
4. Infant must be aged between 4 and 11 months (ie, ≥4 months up to <12 months) on the day of randomization.
5. Infant must be healthy in the investigator's clinical judgment (and the parent(s)/guardian) on the basis of medical history, physical examination, vital signs and clinical laboratory tests performed at screening.

Note: The safety laboratory assessments at screening are to be performed within 28 days prior to the first vaccination on Day 1 (including Day 1 before vaccination) and may be repeated if they fall outside this time window.

Note: If laboratory screening tests are out of range and deemed clinically significant, repeating screening tests to assess eligibility is permitted once during the screening period, using an unscheduled visit.

6. Infant has received all routine immunizations appropriate for his or her age at the time of enrollment as documented in the vaccination cards presented by the parent(s)/guardian. Participants are allowed to catch up on routine immunizations if needed (support for beneficial vaccines may be offered to participants).

7. Parent(s)/guardian is available and willing to have their infant participate for the duration of the study visits and follow-up.

8. Parent(s)/guardian must have a means to be contacted.

9. The parent(s)/guardian must pass the Test of Understanding (TOU) (Appendix 1) (see Section 16.1).

   Note: If the parent(s)/guardian fails the TOU test on the first attempt, he/she must be retrained on the purpose of the study and must take the test again (2 repeats are allowed). If he/she fails on the third attempt, they should not continue with screening or consenting procedures.

4.1.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Having received any candidate or other Ebola vaccine.

2. History of EVD, or prior exposure to Ebola virus, including travel to an area with a current Ebola outbreak less than 1 month prior to screening.

3. Having received any experimental candidate Ad26- or MVA-based vaccine in the past.

   Note: Receipt of any approved vaccinia/smallpox vaccine or experimental Ad-vector vaccine other than Ad26 prior to study entry is allowed.

4. Criterion modified per Amendment 2

   4.1 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 [eg, polysorbate 80, ethylenediaminetetraacetic acid (EDTA) or L-histidine for Ad26.ZEBOV vaccine; tris (hydroxymethyl)-amino methane

(THAM) for MVA-BN-Filo vaccine and *Neisseria meningitidis* polysaccharide or tetanus toxoid for MenACWY]), including known allergy to chicken or egg proteins and aminoglycosides (gentamicin).

5. Criterion modified per Amendment 2

   5.1 Presence of acute illness (this does not include minor illnesses such as mild diarrhea or mild upper respiratory tract infection) or axillary temperature ≥37.5ºC on Day 1. Participants with such symptoms will be excluded from enrollment at that time but may be rescheduled for enrollment at a later date.

6. Weight-for-age z-scores below -2 standard deviations of normal for age according to the WHO growth charts (<1-year-olds).[21]

7. Having been vaccinated with any live-attenuated vaccine within 30 days before the first vaccination, and with any inactivated vaccine within 15 days before the first vaccination.

   Note: Study intervention administration may be rescheduled to allow for infants to receive their routine immunizations and be able to participate in this study.

8. Major congenital anomalies or known genetic disorders, which in the opinion of the investigator or other delegated individual would increase the risk of an adverse outcome from participation in the study.

9. Infant lives in an orphanage or other institution.

10. Significant prematurity or antenatal, perinatal, or early postnatal complications as judged by the investigator or other delegated individuals.

11. Clinically significant history of skin disorder (eg, psoriasis, contact dermatitis), allergy, symptomatic immunodeficiency, cardiovascular disease, respiratory disease, endocrine disorder, liver disease, renal disease, gastrointestinal disease, neurological illness as judged by the investigator or other delegated individual.

12. Criterion modified per Amendment 2

    12.1 Any of the following laboratory abnormalities at screening:

    - Hemoglobin <9.0 g/dL
    - Platelet count <100 x 10^9/L
    - White blood cell count <5.0 x 10^9/L

13. Received a blood transfusion or other blood products within 8 weeks of screening.

14. Any other finding which in the opinion of the investigator or other delegated individual would increase the risk of an adverse outcome from participation in the study.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including receipt of additional medical records) after screening but before the first vaccination (Day 1) is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study.

4.2. Extension Phase

Screening for eligible participants will be performed within 28 days before administration of the study intervention.

The inclusion and exclusion criteria for enrolling participants in the extension phase of the study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the extension phase of the study. Waivers are not allowed.

Note: Participants need to confirm their informed consent for participation in the extension phase.

4.2.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Prior enrollment in the control arm of the main study and did not withdraw consent, and receipt of at least the first vaccination (Dose 1) in the main study.

2. Parent(s) (preferably both if available or as per local requirements)/guardian must sign an ICF indicating that he or she understands the purpose of, and procedures required for the extension phase of the study, and potential risks and benefits of the extension phase of the study and are willing to allow their child to participate in the extension phase of the study.

3. Parent(s)/guardian are willing/able to ensure that their child adheres to the prohibitions and restrictions specified in this protocol (see Section 4.3).

4. The parent(s)/guardian must be at or above the age of legal consent in the jurisdiction in which the study is taking place.

5. Child must be healthy in the investigator's clinical judgment (and the parent(s)/guardian) on the basis of clinical assessment and clinical laboratory tests performed at screening.

   Note: The safety laboratory assessments at screening are to be performed within 28 days prior to the first vaccination on Day 1 (including Day 1 before vaccination) of the extension phase and may be repeated if they fall outside this time window.

   Note: If laboratory screening tests are out of range and deemed clinically significant, repeating screening tests to assess eligibility is permitted once during the screening period, using an unscheduled visit.

Note: Collection of a baseline serum sample for future testing in the event a case of TTS is reported, will not be required. Collection of blood from children that is unlikely to be analyzed, is contrary to conduct of studies in children and unlikely to be approved by Ethics Committees.

6. Parent(s)/guardian is available and willing to have their child participate for the duration of the study extension phase visits and follow-up.

7. Parent(s)/guardian must have a means to be contacted.

8. The parent(s)/guardian must pass the Test of Understanding (TOU) (Appendix 1) (see Section 16.1).

   Note: If the parent(s)/guardian fails the TOU test on the first attempt, he/she must be retrained on the purpose of the extension phase and must take the test again (2 repeats are allowed). If he/she fails on the third attempt, they should not continue with screening or consenting procedures.

4.2.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the extension phase of the study:

1. Having received any candidate or other Ebola vaccine.

2. History of EVD, or prior exposure to Ebola virus, including travel to an area with a current Ebola outbreak less than 1 month prior to screening.

3. Having received any experimental candidate Ad26- or MVA-based vaccine in the past.

   Note: Receipt of any approved vaccinia/smallpox vaccine or experimental Ad-vector vaccine other than Ad26 prior to study entry is allowed.

4. 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 [eg, polysorbate 80, ethylenediaminetetraacetic acid (EDTA) or L-histidine for Ad26.ZEBOV vaccine; tris (hydroxymethyl)-amino methane (THAM) for MVA-BN-Filo vaccine, including known allergy to chicken or egg proteins and aminoglycosides (gentamicin).

5. Presence of acute illness (this does not include minor illnesses such as mild diarrhea or mild upper respiratory tract infection) or axillary temperature ≥37.5ºC on Day 1. Participants with such symptoms will be excluded from enrollment at that time but may be rescheduled for enrollment at a later date.

6. Weight-for-age z-scores below -2 standard deviations of normal for age according to the WHO growth charts.[21]

7. Having been vaccinated with any live-attenuated vaccine within 30 days before the first vaccination in the extension phase of the study, and with any inactivated vaccine within 15 days before the first vaccination in the extension phase of the study.

   Note: Study intervention administration may be rescheduled to allow for infants to receive their routine immunizations and be able to participate in this study.

8. Major congenital anomalies or known genetic disorders, which in the opinion of the investigator or other delegated individual would increase the risk of an adverse outcome from participation in the study.

9. Child lives in an orphanage or other institution.

10. Clinically significant history of skin disorder (eg, psoriasis, contact dermatitis), allergy, symptomatic immunodeficiency, cardiovascular disease, respiratory disease, endocrine disorder, liver disease, renal disease, gastrointestinal disease, neurological illness as judged by the investigator or other delegated individual.

11. Any of the following laboratory abnormalities at screening:
    - Hemoglobin <9.0 g/dL
    - Platelet count <100 x 10^9/L

12. Received a blood transfusion or other blood products within 8 weeks of screening.

13. Any other finding which in the opinion of the investigator or other delegated individual would increase the risk of an adverse outcome from participation in the study.

14. History of any thrombotic disorder, thrombocytopenia, heparin-induced thrombocytopenia and thrombosis (HITT) or TTS.

NOTE: Investigators should ensure that all study extension phase enrollment criteria have been met at screening. If a participant's clinical status changes (including receipt of additional medical records) after screening but before the first vaccination in the extension phase (eDay 1) is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the extension phase of the study.

4.3. Prohibitions and Restrictions

Parent(s)/guardian must be willing and able to adhere to the following prohibitions and restrictions during the course of the study for their child to be eligible for participation:

1. In case of a new Ebola outbreak: participants and parent(s)/guardian must not travel to an area with Ebola outbreak while the participant is enrolled in the study from the start of screening onwards until the 21-day post-dose-2 visit. If applicable, any traveling to

an area with Ebola outbreak should be documented in the case report form (CRF). The date of travel and the destination should be clearly identified.

2. Ensure that their infant does not use any disallowed concomitant therapies as described in Section 8.

Currently, no COVID vaccine is licensed for use in this pediatric age group. During the course of the study, vaccinations may become recommended for this age group. In that case, at least 30 days should elapse between administration of any Ad-based COVID vaccine and Ad26.ZEBOV to avoid any confounding 'carry-over' of adverse events from one vaccine to another. At least 2 weeks should elapse between any mRNA based COVID vaccine and Ad26.ZEBOV.

5. INTERVENTION ALLOCATION AND BLINDING

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention arms based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by country and age group. The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

Blinding

Main Study

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the intervention assignment (ie, study intervention preparation/ accountability data, or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of interim database lock and unblinding. The pharmacy and preparation of study intervention will be monitored by an independent study intervention monitor (see Section 17.9).

Under normal circumstances, the blind should not be broken until all participants have completed the main study and the database is locked. The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contacts the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be

available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded should continue to return for scheduled evaluations.

In general, randomization codes will be disclosed fully only if the last participant has completed the last visit of the main study (follow-up visit 12 months post-dose-1) or has left the main study and the clinical database is locked.

If the randomization code is broken by the investigator or the study-site personnel, the participant must discontinue further study intervention administration and must be followed as appropriate (see Section 10.2 for details). If the randomization code is broken by the sponsor for safety reporting purposes, the participant should not discontinue further study intervention administration and may remain in the study (if the randomization code is still blinded to the study-site personnel and the participant).

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study intervention assigned to the withdrawn participant may not be assigned to another participant. For participants who withdraw from the study after randomization but before the first vaccination, an additional participant will be enrolled who will receive the same vaccination regimen as the withdrawn participant. Participants who withdraw from the study after receiving the first vaccination will not be replaced.

Extension Phase

The extension phase for participants enrolled in the control arm of the main study, will be open label.

6. DOSAGE AND ADMINISTRATION

An overview of the study vaccination schedule is provided in Table 2.

Table 2: Study Vaccination Schedule (Main Study)

N (per arm)	Dose 1 (D1)	Dose 2 (D57)	Third vaccination (6 months post-dose-2)
73	Ad26.ZEBOV $5x10^{10}$ vp	MVA-BN-Filo $1x10^{8}$ Inf U	MenACWY
34	MenACWY	MenACWY	MenACWY

All participants randomized to the Ad26.ZEBOV, MVA-BN-Filo arm will receive the following study vaccines as a 0.5-mL IM injection into the anterolateral thigh:

- Ad26.ZEBOV: $5x10^{10}$ vp on Day 1
- MVA-BN-Filo: $1x10^{8}$ Inf U on Day 57

Participants in the control arm will receive the WHO-prequalified MenACWY as Dose 1 on Day 1, as Dose 2 on Day 57.

The recommended immunization series of MenACWY consists of 2 doses given 2 months apart, followed by a booster dose at 12 months of age. Previously unvaccinated children may receive a single dose in their second year of life. In keeping with the recommended immunization regimen for this vaccine, all participants will receive a dose of MenACWY at the 6-months post-dose-2 visit. The MenACWY vaccine will be administered as a 0.5-mL IM injection into the anterolateral thigh.

Upon completion of the main study, participants in the extension phase who were originally randomized to the control arm will receive the same vaccine regimen as the participants in the Ad26.ZEBOV, MVA-BN-Filo arm of the main study.

In the main study, study intervention will be prepared by an unblinded pharmacist or qualified staff member with primary responsibility for study intervention preparation and dispensing, and who is not involved in any other study-related procedures. Participants will be administered the study intervention in a masked syringe in a way that maintains double-blinding.
In the extension phase, the preparation of the study intervention will be unblinded.

In the main study, Ad26.ZEBOV, MVA-BN-Filo, or MenACWY will be administered as 0.5-mL IM injections in the anterolateral thigh, by a blinded study intervention administrator. In the extension phase, the study intervention administrator will be unblinded, and the vaccine may be administered IM either into the deltoid muscle or in the anterolateral thigh.
The injection site should be free from any injury, local skin conditions, or other issue that might interfere with the evaluation of local reactions. In each participant, the second vaccination should be administered in the opposite leg from the first vaccination (unless the opposite leg has a condition that prevents evaluating the leg after injection) and it should be recorded in the CRF in which leg the vaccination has been administered. The vaccination at 6 months post-dose-2 can be administered in either leg. No local or topical anesthetic will be used prior to the injection.

Discontinuation of study intervention administration should occur in any participant meeting the criteria outlined in Section 10.2. Criteria for postponement of vaccination and contraindications to the second vaccination and MenACWY vaccination at 6 months post-dose-2 are defined in Sections 6.1 and 6.2, respectively. Refer to Section 9.3.2 for details on the pre-specified pausing rules to halt vaccination of further participants.

Participants will remain at the site for at least 30 minutes after each vaccination for presence of any acute reactions, or longer if deemed necessary by the investigator (eg, in case of grade 3 adverse events). As with any vaccine, allergic reactions following vaccination with the study intervention are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available and a medically qualified member of study-site personnel trained to recognize and treat anaphylaxis must be present in the clinic during the entire vaccination procedure and post-vaccination monitoring period.

The investigator must provide emergency care as needed for any participant who experiences a life-threatening event. All sites will have facilities, equipment and the ability to manage an anaphylactic reaction. If additional therapy is required, the investigator will arrange for transport to the closest appropriate facility for continuing care.

The Site Investigational Product Procedures Manual specifies the maximum time that will be allowed between preparation and administration of the study intervention.

Ad26.ZEBOV and MVA-BN-Filo will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.[14]

6.1. Criteria for Postponement of Vaccination

A participant will not be given any vaccination if he/she experiences any of the following events at the scheduled time for vaccination:

- Acute illness at the time of vaccination (this does not include minor illnesses such as diarrhea or mild upper respiratory tract infection);
- Axillary temperature ≥37.5°C at the time of vaccination.

Participants experiencing any of the events described above may be vaccinated up to 10 days beyond the window allowed for the scheduled vaccination or be withdrawn from that vaccination at the discretion of the investigator and after consultation with the sponsor.

Note: In case the second vaccination is postponed, the timing of the post-dose-2 visits will be planned relative to the actual vaccination day.

6.2. Contraindications to Second Vaccination and 6-months Post-dose-2 Vaccination

A participant will not be given the second vaccination or the MenACWY vaccination at 6 months post-dose-2 if he/she experiences any of the following events at any time after the first vaccination:

1. Anaphylaxis clearly attributable to vaccination with study intervention; *OR*
2. Generalized urticaria within 24 hours of vaccination considered to be related to study intervention; *OR*
3. A serious adverse event considered to be related to study intervention; *OR*
4. Injection site ulceration, abscess, or necrosis considered to be related to study intervention; *OR*
5. Any other safety concern threatening the participant’s safety.

Participants experiencing any of the events described above must not receive any further study intervention but should be monitored for safety and for immunogenicity according to the protocol.

7. INTERVENTION COMPLIANCE

In the main study, study intervention will be administered as an IM injection by blinded qualified study-site personnel at the study site. Details of each administration will be recorded in the CRF (including date and time of injection and thigh used for injection). For blinding procedures, see Section 5. In the extension phase, study intervention will be administered by unblinded qualified study-site personnel.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy therapies administered up to 30 days prior to the start of screening and previous vaccinia/smallpox vaccination at any time prior to study entry must be recorded in the CRF at screening for the main study.

Infants in the main study and children in the extension phase must receive all routine immunizations appropriate for their age according to local routine vaccination schedules, taking into consideration the following restrictions. A participant should not receive a live-attenuated vaccine from 30 days before the first vaccination until 30 days after the second vaccination unless a vaccine preventable disease such as measles emerges which would warrant administration of live-attenuated vaccines. Immunizations with inactivated vaccines should be administered at least 15 days before or after administration of any study intervention in order to avoid any potential interference in efficacy of the routine immunizations or the interpretation of immune responses to study intervention, as well as to avoid potential confusion with regard to attribution of adverse reactions. However, if a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study intervention. Otherwise, a participant will not postpone, forego, or delay the receipt of any recommended vaccine according to local schedules (eg, EPI schedule according to the WHO regional office for West Africa). Prior to vaccination of infants in the main study and children in the extension phase, parent(s)/guardian will be asked to show the child's EPI vaccination card to check that the child has not received a live-attenuated vaccine within the last 30 days. In case the parent(s)/guardian does not have a card or cannot show it, the participant will be excluded from the study.

Considering the COVID-19 situation, administration of COVID-19 vaccine should follow the national guidelines and schedule. COVID-19 vaccine may be prioritized or intercalated with Ebola vaccination according to national guidance by authorities. Recombinant viral vectored COVID-19 vaccines or live attenuated COVID-19 vaccines, either licensed or authorized for emergency use (eg, Emergency Use Authorization [EUA], Emergency Use Listing [EUL] or similar program) should not be administered within 30 days before or after planned administration of the study intervention. Other COVID-19 vaccines that are not viral vectored, or are not live attenuated, (eg, mRNA vaccines, protein-based vaccines) either licensed or authorized for emergency use (eg, EUA, EUL or similar program) should not be administered within 15 days before or after planned administration of the study intervention.

Note: National Immunization Plans will be available on site and these will be taken into consideration when planning vaccination schedules. Study intervention administration may be

rescheduled to allow for infants to receive their routine immunizations and be able to participate in this study.

Analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs may be used post-vaccination in case of medical need (eg, fever or pain). Use of these medications as routine prophylaxis prior to study intervention administration is not recommended. The use of these medications must be documented.

Concomitant therapies must be recorded from screening onwards until 28 days post-dose-1 and from the second vaccination until 28 days post-dose-2. At the other time points, they should only be recorded if given in conjunction with serious adverse events. Information on concomitant use of herbal supplements or vitamins will not be collected, except for the use of vitamin A supplementation, which will be collected.

Use of any experimental medication (including experimental vaccines other than the study intervention) during the study is not allowed.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of safety and immunogenicity measurements applicable to this study. Details for all study procedures are provided in the following sections. Additional unscheduled study visits may be required if in the investigator's opinion, further clinical or laboratory evaluation is needed.

Visit Windows

Visit windows are provided in the Time and Events Schedule. If a participant did not receive study intervention on the planned day of vaccination, the timings of the next visits post-vaccination will be determined relative to the actual day of vaccination. The participant should be encouraged to come within these windows.

Blood Sampling Volume

Main Study

The total blood volume for the main study is 8.0-9.5 mL: 2.0 mL for safety and 6.0-7.5 mL for immunogenicity depending on the most successful phlebotomy method, either the direct (vacutainer) method or indirect (syringe) method. If the indirect (syringe) method is chosen, the immunogenicity blood sample is 2.0 mL per visit and the total blood volume is 8 mL. If the direct (vacutainer) method is chosen, then the immunogenicity blood sample is 2.5 mL per visit and the

total blood volume is 9.5 mL. Whenever feasible, a single phlebotomy method will be used for a given subject.

The maximum amount of blood that will be drawn on a single visit is 3.5 mL. The study-related blood volumes obtained (including any losses during phlebotomy) will not exceed 3% of the total blood volume during a period of 4 weeks and will not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90 mL/kg body weight; 3% is 2.4 mL blood per kg body weight.[9] The allowable blood volume calculations are based on the 10th percentile for growth charts for infants.[21]

Extension Phase

In the extension phase a total blood volume of 2.0 mL will be drawn for safety laboratory assessments, ie, 1 mL at screening and 1 mL prior to administration of MVA-BN-Filo.

In the unlikely event that a TTS event should occur after Dose 1 administration, pre-existing anti-PF4 antibodies may be assessed in the baseline serum of the participant.

For details on the approximate blood sampling volumes collected by visit and the cumulative blood volumes, refer to the Time and Events Schedule.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening Period

Main Study

Up to 28 days before baseline (Day 1, day of first vaccination) and after signing and dating the ICF (see Section 16.2.3), screening assessments will be performed as indicated in the Time and Events Schedule. Screening may be split into multiple days or visits.

Only participants complying with the criteria specified in Section 4 will be included in the study. The investigator will provide detailed information on the study to the parent(s)/guardian of the infant and will obtain written informed consent from them prior to study participation of the infant.

After reading but before signing the ICF, the TOU will be administered to the parent(s)/guardian. Parent(s)/guardian who fail may repeat the test twice (and have to pass the third time for their child to be eligible) (for details, see Section 16.1).

The overall eligibility of the participant to participate in the study will be assessed once all screening values and results of any other required evaluations are available. Retesting of values (eg, safety laboratory, weights that are at the borderline of the z-scores at screening) that lead to exclusion is allowed once using an unscheduled visit during screening to assess eligibility. If rescreening is required, all screening procedures (except TOU) should be repeated. Study participants who qualify for inclusion will be contacted and scheduled for enrollment and first vaccination within 28 days.

A serum sample will be taken at screening, to serve as pre-vaccination baseline sample for immunogenicity assessments (see Section 9.4).

Extension Phase

For participation in the extension phase of the study, a separate ICF and TOU will need to be signed. The screening procedures are the same as in the main study, except that no serum sample will be taken at screening to serve as pre-vaccination baseline sample for immunogenicity assessments.

9.1.3. Vaccination Period

If eligible, the participant will come for the baseline visit (Day 1). The investigator should ensure that all enrollment criteria have been met during screening. If a participant's clinical status changes (including available laboratory results or receipt of additional medical records) after screening but before the first vaccination (Day 1) such that he/she no longer meets all enrollment criteria, then the participant should be excluded from further participation in the study.

Eligible participants will be allocated to an intervention arm as described in Section 5. Before each vaccination, a brief physical examination (including body length and weight) and measurement of vital signs will be performed.

Participants will be vaccinated as described in Section 6. After each vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions, or longer if deemed necessary by the investigator. Following the first and second vaccination, any unsolicited, solicited local or systemic adverse events, and vital signs will be documented by study-site personnel at the end of this observation period.

Upon discharge from the site, parent(s)/guardian will be provided with a thermometer (to measure body temperature), a ruler (to measure local injection site reactions), and a participant diary to record body temperature and solicited local (at injection site) and systemic symptoms and will be trained on how to collect this information. Symptoms of solicited local and systemic adverse events will be collected in the diary in the evening after the first and second vaccination and then daily for the next 7 days at approximately the same time each day. Diaries will be completed at home by either a project field worker who will visit the participant during daily visits or by the parent(s)/guardian and checked by a project field worker. The investigator or clinical designee will review information from the participant's diary.

Participants will come to the site at 7 days after the first and second vaccination as indicated in the Time and Events Schedule. The participant's diary will be reviewed by study-site personnel. The investigator will examine the injection site for occurrences of erythema, swelling, or tenderness at these visits in order to complete the relevant parts of the CRF.

Unsolicited adverse events will be reported from the first vaccination until 28 days post-dose-1, and from the second vaccination until 28 days post-dose-2.

Serious adverse events and/or special reporting situations that are related to study procedures or that are related to non-investigational (concomitant) sponsor products will be reported from the time a signed and dated ICF is obtained onwards until the end of the study. All other serious adverse events and/or special reporting situations will be reported from the day of first vaccination onwards until 6 months post-dose-2 for the main study, and for 28 days post-dose-2 for the extension phase.

Participants will come to the site at 21 days after the second vaccination for safety and immunogenicity assessments. Refer to Section 9.4 for details on the immunogenicity evaluations.

In the main study, the parent(s)/guardian will be instructed to contact the investigator before the next visit (ie, 6 months post-dose-2) if their child experiences any adverse event or intercurrent illness that they perceive as relevant and/or can be possibly related to study intervention in their opinion.

All participants will receive a dose of MenACWY at 6 months post-dose-2 in the main study as described in Section 6. After vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions, or longer if deemed necessary by the investigator. Vital signs will also be collected at the end of the observation period. Participant diaries will not be distributed. Infants that experience any symptoms will be invited to come for an unscheduled visit as needed.

No immunogenicity assessments will be performed in the extension phase.

9.1.4. Follow-up Period

Participants of the main study will return to the study site at 12 months post-dose-1 to check for serious adverse events related to study intervention, and to collect a blood sample for immunogenicity assessments (see Section 9.4).

9.2. Procedures in Case of a Study Pause

A study pause can affect participants that are either awaiting the first or second vaccination. After approval is granted to restart the study, participants who are awaiting the first vaccination and whose screening period is longer than the protocol-defined 28 days as a result of a study pause, will be allowed to rescreen once (following the screening procedures described in Section 9.1.2, excluding TOU). Participants that are rescreened due to a pause must have new safety laboratory assessments (including full blood count, physical examination, and vital signs) within 28 days of the first vaccination. The TOU does not need to be repeated. After screening, these participants will follow the same study procedures as those participants who were unaffected by a study pause (described in Section 9.1.3).

Participants who are outside the protocol-defined second vaccination window due to a study pause will be offered a late second vaccination (if allowed by the sponsor and/or the relevant oversight authorities). Participants who will receive a late second vaccination will follow the same post-dose-2 vaccination schedule as those participants whose second vaccination was unaffected by a

study pause (see Section 9.1.3). In case the second vaccination is postponed, the timing of the post-dose-2 visits will be planned relative to the actual vaccination day.

9.3. Safety Evaluations

9.3.1. Safety Assessments

The investigators, together with the sponsor's medical monitor, will be responsible for the safety monitoring of the study, and will halt vaccination of further participants in case any of the pre-specified pausing rules described in Section 9.3.2 have been met. Further safety measures with regards to vaccination are described in Sections 6.1 and 6.2.

An IDMC will be appointed by the sponsor before the start of the main study to perform regular review of the safety data during the study. Details regarding the IDMC are provided in Section 11.7. In the extension phase, the IDMC will be replaced by an independent medical reviewer. Details regarding the independent medical reviewer are provided in Section 11.8.

Symptoms of solicited local and systemic adverse events will be collected in the diary in the evening after the first and second vaccination and then daily for the next 7 days. Unsolicited adverse events will be collected from the first vaccination until 28 days post-dose-1, and from the second vaccination until 28 days post-dose-2. Serious adverse events and/or special reporting situations that are related to study procedures or that are related to non-investigational (concomitant) sponsor products will be reported from the time a signed and dated ICF is obtained onwards until the end of the study phase (main and extension phase). All other serious adverse events and/or special reporting situations will be reported from the day of the first vaccination onwards until 6 months post-dose-2 in the main study, and until 28 days post-dose-2 in the extension phase.

Any clinically relevant changes must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

All AEs will be coded for severity according to the criteria presented in Section 12.1.3.

The study will include the following evaluations of safety and reactogenicity according to the time points provided in the Time and Events Schedule:

Adverse Events

Adverse events will be reported as specified in Section 12.3.1.

Solicited Adverse Events

After each vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions, or longer if deemed necessary by the investigator. Symptoms of solicited local and systemic adverse events will be collected in the diary in the evening after the first and second vaccination and then daily for the next 7 days. Diaries will be

completed at home by either a project field worker who will visit the participant during daily visits or by the parent(s)/guardian and checked by a project field worker. Diary information will be transcribed by the study personnel in the diary CRF pages. Once a solicited symptom from a diary is considered to be of severity Grade 1 or above, it will be referred to as a solicited adverse event.

Solicited Injection Site (Local) Adverse Events

Parents/guardians (or the project field worker) will be asked to note in the diary occurrences of tenderness, erythema and swelling at the study intervention injection site daily for 7 days post-vaccination (day of vaccination and the subsequent 7 days). The extent (largest diameter) of any erythema, and swelling should be measured (using the ruler supplied) and recorded daily.

- **Injection Site Tenderness**

Injection site tenderness is a painful sensation localized at the injection site upon palpation or movement of the limb. Due to subjective nature of the reaction, the severity assessment of tenderness is self-reported (if a participant is unable to provide self-report, other reporters include parent/care giver or health care provider).[11]

- **Injection Site Erythema**

Injection site erythema is a redness of the skin caused by dilatation and congestion of the capillaries localized at the injection site. It can best be described by looking and measuring.

- **Injection Site Swelling**

Injection site swelling is a visible enlargement of an injected limb. It may be either soft (typically) or firm (less typical).

Note: Any other injection site events not meeting the above case definitions should be reported separately as unsolicited AEs.[18]

Solicited Systemic Adverse Events

Parent(s)/guardian will be instructed on how to record daily temperature using a thermometer provided for home use. The axillary temperature of the participant should be recorded in the diary in the evening of the day of vaccination, and then daily for the next 7 days at approximately the same time each day. If more than one measurement is made on any given day, the highest temperature of that day will be used in the CRF.

Fever is defined as endogenous elevation of body temperature ≥38° C, as recorded in at least one measurement.[19]

Parent(s)/guardian will also be instructed on how to note daily in the diary symptoms for 7 days post-vaccination (day of vaccination and the subsequent 7 days) of the following events: loss of appetite, vomiting, diarrhea, decreased activity, irritability.

Physical Examination

A brief, symptom-directed examination (including body length and weight) will be performed based on any clinically relevant issues, clinically relevant symptoms and medical history. The symptom-directed physical examination may be repeated if deemed necessary by the investigator. Physical examinations will be performed by the investigator or by a designated medically-trained clinician. Physical examination findings (ie, abnormalities) prior to Dose 1 vaccination are to be recorded as medical history, after Dose 1 vaccination as adverse event.

Vital Signs

Axillary temperature, pulse/heart rate (beats per minute), and respiratory rate (breaths per minute) will be assessed.

Pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. Pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions.

Clinical Laboratory Tests

Samples will be collected for hematology. The investigator must review the laboratory report, document this review, and record any clinically relevant changes on the adverse event page of the CRF. Laboratory reports must be filed with the source documents.

A full blood count will be performed by the local laboratory at the time points indicated in the Time and Events Schedule:

-hemoglobin
-hematocrit
-red blood cell (RBC) count
-white blood cell (WBC) count with differential
-platelet count

Note: a WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, or RBC morphology, which will then be reported by the laboratory.
In addition, any other abnormal cells in a blood smear will also be reported.

9.3.2. Study Pausing Rules

The investigators and the sponsor's medical monitor will review the safety of enrolled participants on an ongoing basis and will halt vaccination of further participants in case any of the pre-specified pausing rules described in this section are met. The sponsor's medical monitor will be involved in all discussions and decision. These pausing rules are not applicable for the vaccination with MenACWY at 6 months post-dose-2.

If any of the following events occur in any participant who received at least one dose of study intervention in the study (at any site), the site investigator will halt the vaccination of further participants in this study and the sponsor's medical monitor will be notified immediately. The sponsor's medical monitor will inform all the other investigators to halt further vaccination as well.

1. Death of a participant, considered related to study intervention or if the causal relationship to the study intervention cannot be excluded; *OR*

   Note: All cases of death will be sent for IDMC information. Upon their review, IDMC may then also decide whether a study pause is required.

2. One or more participants experience a life-threatening or serious adverse event (solicited or unsolicited) that is determined to be related to study intervention; *OR*
3. One or more participants experience anaphylaxis or generalized urticaria within 24 hours of vaccination, clearly not attributable to other causes than vaccination with study intervention; *OR*
4. Two or more participants experience a grade 3 or 4 unsolicited adverse event of the same type (as per medical judgment of the sponsor), that is determined to be related to study intervention; *OR*
5. Two or more participants experience a grade 3 or 4 solicited systemic adverse event of the same type, determined to be related to study intervention, and persisting for 3 or more days[a]. *OR*
6. Two or more participants experience a grade 3 or 4 local adverse event (including injection site ulceration, abscess or necrosis) of the same type, and persisting for 3 or more days.

For numbers 4, 5, and 6: after each IDMC review of similar adverse events, the Committee will indicate the conditions under which it requires further notification and review of the subsequent similar adverse events.

To enable prompt response to a situation that could trigger pausing rules, the investigator should notify the sponsor's medical monitor or designee (AND fax or email serious adverse event form to Global Medical Safety Operations, if applicable), immediately and no later than 24 h after becoming aware of any related adverse event of grade 3 or above AND update the CRF with relevant information on the same day the adverse event information is collected. A thorough analysis of all grade 3 cases will be carried out by the sponsor's medical monitor or designee, irrespective of whether the criteria for pausing the study are met. Based on the pausing criteria, the sponsor's medical monitor or designee then decides whether a study pause is warranted. All investigators will be notified immediately in case of a study pause. The sponsor's medical monitor or designee is responsible for the immediate notification of IDMC members and coordination of an IDMC meeting in case of a study pause.

Vaccinations for an individual participant may be suspended for safety concerns other than those described in the pausing criteria, at the discretion of the investigator if he/she feels the participant's safety may be threatened. The sponsor's medical monitor or designee or the investigator(s) (upon consultation with the sponsor's medical monitor or designee) may initiate IDMC review for any

[a] The day of occurrence of the adverse event is counted as Day 1.

single event or combination of multiple events which, in their professional opinion, could jeopardize the safety of the participants or the reliability of the data.

Vaccinations for the study may be suspended for safety concerns other than those described above, or before pausing rules are met, if, in the judgment of the IDMC, participant safety may be threatened.

Resumption of vaccinations will start only upon receipt of written recommendations by the IDMC. The clinical site(s) will be allowed to resume activities upon receipt of a written notification from the sponsor. The communications from the IDMC will be forwarded by the investigator to the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and by the sponsor to the relevant health authorities, according to local standards and regulations.

In the extension phase of the study, the IDMC will be replaced by an independent medical reviewer (see Section 11.8).

9.4. Immunogenicity Assessments

In the main study, venous blood samples (2.0-2.5 mL) for the determination of immune responses will be collected at the time points indicated in the Time and Events Schedule. Serum will be used for the following assessments:

- Analysis of binding antibodies against EBOV GP (FANG ELISA): to determine humoral responses following vaccination.
- Analysis of neutralizing antibody response against the adenovirus backbone (Ad26 VNA): to explore baseline neutralizing antibody responses against the vector in the study population.

Sample collection and processing will be performed by the study-site personnel according to current versions of approved standard operating procedures. The Laboratory Manual contains further details regarding the collection, handling, labeling, and shipment of blood samples to the respective laboratories.

During the extension phase, no blood samples for immunogenicity evaluations will be collected.

9.5. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form.

Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

10. PARTICIPANT COMPLETION/DISCONTINUATION OF STUDY INTERVENTION/ WITHDRAWAL FROM THE STUDY

10.1. Completion

Main Study

A participant will be considered to have completed the main study if he or she has completed all assessments at the 12-months post-dose-1 visit.

Participants who prematurely discontinue study participation for any reason before completion of the 12-month post-dose-1 visit will not be considered to have completed the main study.

A participant in the Ebola vaccine arm of the main study will be considered to have completed the study if he or she has completed all assessments at the 12-months post-dose-1 visit.

Extension Phase

A participant will be considered to have completed the extension phase of the study if he or she has completed all assessments at the 28 days post-dose-2 visit.

Participants who prematurely discontinue study participation for any reason before completion of the 28 days post-dose-2 visit will not be considered to have completed the extension phase of the study.

A participant of the extension phase will be considered to have completed the study if he or she has completed both the main study and the extension phase.

10.2. Discontinuation of Study Intervention/Withdrawal From the Study

Discontinuation of Study Intervention

A participant will not be automatically withdrawn from the study if he or she has to discontinue study intervention before the end of the intervention regimen.

A participant's study intervention (dose 1 or dose 2) must be discontinued at the discretion of the investigator and after consultation with the sponsor for any of the events in Section 6.1.

A participant's study intervention should be **permanently** discontinued if:

- The investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the participant to discontinue study intervention;
- Confirmed EVD
- The participant experiences any of the events described in Section 6.2;
- The randomization code is broken by the investigator or the study-site personnel (only applicable for main study).

Participants meeting any of the reasons listed above must not receive any further study intervention, but should continue to be monitored for safety and immunogenicity according to the protocol if this does not result in safety risks for the participant. In case of early discontinuation of study intervention due to an adverse event, the investigator will collect all information relevant to the adverse event and safety of the participant, and will follow the participant to resolution, or until reaching a clinically stable endpoint. In case of a study pause, participants need to follow procedures as described in Section 9.2.

Withdrawal From the Study

Parent(s)/guardian have the right to withdraw their child from the study at any time for any reason without affecting the right to treatment by the investigator. The investigator should make an attempt to contact participants who did not return for scheduled visits or follow-up. Although parent(s)/guardian are not obliged to give reason(s) for withdrawing prematurely, the investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the participant's rights.

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death
- Repeated failure to comply with protocol requirements
- Decision by the sponsor or the investigator to stop or cancel the study
- Decision by local regulatory authorities or IEC/IRB to stop or cancel the study

If a participant is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the participant and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. For participants who withdraw from the study after randomization but before the first vaccination, an additional participant will be enrolled who will receive the same vaccination regimen as the withdrawn participant. Participants who withdraw from the study after receiving the first vaccination will not be replaced.

Participants who wish to withdraw consent from participation in the study will be offered an optional visit for safety follow-up (prior to formal withdrawal of consent). They have the right to refuse.

Withdrawal From the Use of Samples in Future Research

Parent(s)/guardian may withdraw consent for use of their child's samples for research (refer to Section 16.2.5). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the safety and immunogenicity data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

The primary interim analysis for the blinded phase of the study will be done when all participants have completed the 12 months post-dose-1 visit or have left the main study (ie, completion of the main study), and the clinical database is locked and unblinded. This analysis will include all available data up to the 12 months post-dose-1 (D365) visit.

The final analysis will be performed at study completion, defined as the date of final database lock, which will occur after all participants have completed the last study-related visit or left the study.

11.1. Analysis Sets

Full Analysis Set: The full analysis set will include all randomized participants with at least one study intervention administration documented. Participants will be analyzed according to the intervention they actually received.

Per-protocol Immunogenicity Population: The per-protocol immunogenicity population will include all randomized and vaccinated participants for whom immunogenicity data are available excluding participants with major protocol deviations expecting to impact the immunogenicity outcomes (eg, missed vaccinations, natural infections, etc).

11.2. Sample Size Determination

The sample size is not based on formal hypothesis testing considerations. Active control recipients are included for blinding purposes and safety analyses, and will provide control specimens for immunologic assays.

The sample size for this study expands the safety and immunogenicity database for VAC52150 to infants. While mild to moderate vaccine reactions (local/systemic responses) are expected, adverse events that preclude further study intervention administration or more serious events that would limit product development are not anticipated:

- When 73 infants are vaccinated with Ad26.ZEBOV, MVA-BN-Filo, the observation of 0 reactions would be associated with a 95% confidence that the true rate is less than 4.0%.
- When 34 infants are vaccinated with active control, the observation of 0 reactions would be associated with a 95% confidence that the true rate is less than 8.4%.

Table 3 provides the probabilities of observing at least one adverse event at given true adverse event rates.

Table 3: Probability of Observing at Least One Adverse Event Given a True Adverse Event Incidence

	Probability of Observing at Least One Adverse Event (%)	
True Adverse Event Incidence (%)	Ad26.ZEBOV, MVA-BN-Filo N=73	Active Comparator N=34
1	52	29
3	89	64
5	98	83
7	99	92
9	100	96
15	100	100

n: number of participants

11.3. Participant Information

For all participants, demographic characteristics (eg, age, weight and length percentiles according to WHO pediatric growth and weight charts,[21] race, and gender), and other baseline characteristics (eg, vital signs, concomitant diseases) will be tabulated and summarized with descriptive statistics.

11.4. Safety Analyses

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively (including 95% CIs, if applicable) by intervention arm.

Adverse Events (Including Reactogenicity)

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events and events-related diary information (solicited local at injection site and systemic, and unsolicited) with onset within 28 days after the first or second vaccination (ie, intervention-emergent adverse events) will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention arm.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue study intervention due to an adverse event, or who experience a severe or a serious adverse event.

Physical Examination

Because only abbreviated, symptom-directed examinations are performed per discretion of the investigator, physical examination findings (ie, abnormalities) after Dose 1 vaccination are to be recorded as adverse events, and will be analyzed and presented as indicated above. When reported prior to Dose 1 vaccination, they will be recorded as medical history.

Baseline percentiles of body length and weight (according to WHO growth charts, see Section 4) will be tabulated and summarized descriptively (as part of the demographics and baseline characteristics summaries and listings).

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, and respiratory rate values will not be summarized at each scheduled time point. A listing of participants with clinically significant abnormal values will be provided.

Clinical Laboratory Tests

Laboratory abnormalities will be determined according to the toxicity grading tables (see Appendix 2), and in accordance with the normal ranges of the clinical laboratory. The most severe laboratory abnormalities following vaccination will be listed.

11.5. Immunogenicity Analyses

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (geometric mean and 95% CI, or median and range Q1-Q3, as appropriate) will be calculated for continuous immunologic parameters at all available time points. Graphical representations of immunological parameters will be made as applicable. Frequency tabulations will be calculated for discrete (qualitative) immunologic parameters as applicable.

11.6. Interim Analysis

The primary interim analysis for the blinded phase of the study will be done when all participants have completed the 12 months post-dose-1 visit or have left the main study (ie, completion of the main study), and the clinical database is locked and unblinded. This analysis will include all available data up to the 12 months post-dose-1 (D365) visit.

11.7. Independent Data Monitoring Committee

An IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the participants enrolled in the main study.

The Committee will meet periodically to review newly generated data. Ad hoc IDMC meetings may be requested via the sponsor for any single event or combination of multiple events which are considered to jeopardize the safety of the participants. After the review, the IDMC will make recommendations regarding the continuation of the study. The IDMC responsibilities, authorities, frequency and timing of the evaluations and procedures will be documented in its charter. All analyses that are planned to support the IDMC evaluations will be included in the associated SAP.

All IDMC members will be external and independent of the sponsor, including at least one medical expert in the relevant therapeutic area and at least one statistician.

11.8. Independent Medical Reviewer

An independent medical reviewer will be appointed before the start of the extension phase to review the accumulating safety data on an ongoing basis to ensure the continuing safety of the participants enrolled in the extension phase of the study.

The independent medical reviewer will be consulted periodically to review newly generated data. Ad hoc meetings may be requested via the sponsor if any of the pre-specified pausing rules for this study are met (see Section 9.3.2) or in any situation that could affect the safety of the participants.

After the review, the independent medical reviewer will make recommendations regarding the continuation of the extension phase of the study. The independent medical reviewer responsibilities, authorities, frequency and timing of the evaluations and procedures will be documented in a role and responsibility description.

The independent medical reviewer will be external and independent of the sponsor. He or she will be a medical expert in the relevant field.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the participant's parent(s)/guardian is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events

Solicited adverse events are predefined local (at the injection site) and systemic events for which the participant's parent(s)/guardian is specifically questioned, and which are noted in the participant's diary.

Unsolicited Adverse Events

Unsolicited adverse events are all adverse events for which the participant's parent/guardian is not specifically questioned in the participant diary.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related

to that medicinal (investigational or non-investigational) product. (Definition per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures.

Note: For time period of sponsor's adverse event collection, see Section 12.3.1.

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a SUSAR (even after the study is over, if the sponsor, IDMC, independent medical reviewer or investigator becomes aware of them).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For Ad26.ZEBOV and MVA-BN-Filo, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For MenACWY, refer to the applicable vaccine prescribing information.

Adverse Event Associated With the Use of the Intervention

An adverse event is considered associated with the use of the intervention if the attribution is related by the definitions listed in Section 12.1.2.

An adverse event is considered not associated with the use of the intervention if the attribution is unrelated by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Every effort should be made by the investigator to explain any adverse event and to assess its potential causal relationship, ie, to administration of the study intervention or to alternative causes (eg, natural history of an underlying diseases, concomitant therapies). This applies to all adverse events, whether serious or non-serious.

Causality of adverse events should be assessed by the investigator based on the following:

Related: there is suspicion that there is a relationship between study intervention and adverse event (without determining the extent of that probability); there is a reasonable possibility that the study intervention contributed to the adverse event. All adverse events assessed as possibly, probably or definitely related to the study intervention will be considered related to the study intervention.

Unrelated: there is no suspicion that there is a relationship between the study intervention and the adverse event; there are other more likely causes and administration of the study intervention is not suspected to have contributed to the adverse event. All adverse event assessed as unrelated or doubtfully related to the study intervention will be considered unrelated to the study intervention.

By definition, all solicited adverse events at the injection site (local) will be considered related to the study intervention administration.

12.1.3. Severity Criteria

All adverse events, except for solicited adverse events, will be coded for severity using a modified version of the Division of Microbiology and Infectious Diseases (DMID) pediatric grading table (November 2007) (see Appendix 2)[8].

For adverse events not identified in the table, the following guidelines will apply:

Mild	Grade 1	Symptoms causing no or minimal interference with usual social and functional activities.
Moderate	Grade 2	Symptoms causing greater than minimal interference with usual social and functional activities.
Severe	Grade 3	Symptoms causing inability to perform usual social and functional activities.
Potentially Life-threatening	Grade 4	Any grade 3 symptom that requires hospitalization/in-patient medical intervention.

Note: Only clinically significant abnormalities in laboratory data occurring from signing of the ICF onwards will be reported as adverse events and graded using the table above.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant.

12.2. Special Reporting Situations

Safety events of interest on a sponsor study intervention that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Medication error involving a sponsor product (with or without participant exposure to the sponsor study intervention, eg, name confusion)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

Symptoms of solicited local and systemic adverse events will be collected in the diary in the evening after the first and second vaccination and then daily for the next 7 days. Unsolicited adverse events will be reported from the first vaccination until 28 days post-dose-1, and from the second vaccination until 28 days post-dose-2.

Serious adverse events and/or special reporting situations that are related to study procedures or that are related to non-investigational (concomitant) sponsor products will be reported from the time a signed and dated ICF is obtained onwards until the end of the study. All other serious adverse events and/or special reporting situations will be reported from the day of the first vaccination onwards until 6 months post-dose-2 in the main study and until 28 days post-dose-2 in the extension phase. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

The investigator will monitor and analyze the study data including all adverse event and clinical laboratory data as they become available and will make determinations regarding the severity of the adverse experiences and their relation to study intervention. All adverse events will be deemed related to study intervention or not related to study intervention, according to Section 12.1.2.

The investigator or clinical designee must review both post-injection reactogenicity and other adverse event CRFs to insure the prompt and complete identification of all events that require expedited reporting as serious adverse events, invoke pausing rules or are other serious and unexpected events.

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common

etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

The parent(s)/guardian will be provided with a "wallet (study) card" and instructed to carry this card with their child for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind
- Ebola prevention counseling

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes

- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

During the entire study, the cause of death of a participant in a study, whether or not the event is expected or associated with the study intervention, is considered a serious adverse event.

12.3.2.1. Thrombosis with Thrombocytopenia Syndrome

As described in Section 1.3.4, TTS has been observed very rarely following vaccination with Janssen COVID-19 vaccine. TTS is a syndrome characterized by a combination of both a thrombotic event and thrombocytopenia.[2,5]

Because this syndrome is rare and not completely understood, all cases of thrombosis and/or thrombocytopenia will be considered a potential case of TTS and should be reported to the sponsor within 24 hours of awareness as a serious adverse event. Each potential event will be reviewed to identify a TTS case. A potential TTS case is defined as:

- Thrombotic events: suspected deep vessel venous or arterial thrombotic events as detailed in Appendix 3,

  and/or

- Thrombocytopenia, defined as platelet count below the lower limit of normal for the testing lab.

Symptoms, signs, or conditions suggestive of a thrombotic event or thrombocytopenia should be recorded and reported to Janssen even if the final or definitive diagnosis has not yet been determined, and alternative diagnoses have not yet been eliminated or shown to be less likely. Follow-up information and final diagnoses, if applicable, should be submitted to the sponsor as soon as they become available.

In the event of thrombocytopenia, study site personnel should report the absolute value for the platelet count and the reference range for the laboratory test used. Any potential events may require enhanced data collection and evaluation. For example, Janssen may request that a platelet count and/ a serum sample for advanced testing be obtained. Every effort should be made to report as much information as possible about the event to Janssen in a reasonable timeframe.

If an event meets the criteria for a serious adverse event (Section 12.1.1), it should be reported using the same process as for other serious adverse events.

Treatment and Follow-up Recommendation

The medical management of thrombotic events with thrombocytopenia is different from the management of isolated thromboembolic diseases. Study site personnel and/or treating physicians should follow available guidelines for treatment of thrombotic thrombocytopenia (eg, American Society of Hematology 2021[2]; British Society of Haematology 2021[6]; CDC 2021[7]). The use of heparin may be harmful and alternative treatments may be needed. Consultation with a hematologist is strongly recommended.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY INTERVENTION INFORMATION

14.1. Physical Description of Study Intervention

14.1.1. Ad26.ZEBOV

Ad26.ZEBOV is a monovalent, replication-incompetent Ad26-based vector that expresses the full-length EBOV Mayinga GP and is produced in the human cell line PER.C6®.

The Ad26.ZEBOV vaccine will be supplied at a concentration of $1x10^{11}$ vp/mL in 2-mL single-use glass vials as a frozen liquid to be thawed before use. Each vial contains an extractable volume of 0.5 mL. Refer to the Investigator's Brochure for a list of excipients.[14]

The Ad26.ZEBOV vaccine is manufactured by IDT Biologika GmbH for Janssen Vaccines & Prevention B.V., The Netherlands.

14.1.2. MVA-BN-Filo

MVA-BN-Filo is a recombinant multivalent vaccine intended for active immunization against Ebola and Marburg virus infection. MVA-BN-Filo is strongly attenuated; the vaccine is propagated in primary chicken embryo fibroblast cells and does not replicate in human cells.

The MVA-BN-Filo vaccine is supplied at a concentration of 2×10^8 Inf U/mL in 2-mL single-use glass vials as a frozen liquid suspension to be thawed before use. Each vial contains an extractable volume of 0.5 mL. Refer to the Investigator's Brochure for a list of excipients.[14]

The MVA-BN-Filo vaccine is manufactured by IDT Biologika GmbH for Janssen Vaccines & Prevention B.V., The Netherlands.

14.1.3. MenACWY

MenACWY is a WHO-prequalified Meningococcal Group A, C, W135 and Y conjugate vaccine.

The MenACWY vaccines will be supplied as commercially available vaccines. Refer to the Summary of Product Characteristics for a list of excipients.

14.2. Packaging

All study intervention will be manufactured and packaged in accordance with Good Manufacturing Practice (GMP). All study intervention will be packaged and labeled under the responsibility of the sponsor. No study intervention can be repacked or relabeled without prior approval from the sponsor.

Further details for study intervention packaging and labeling can be found in the Site Investigational Product Procedures Manual.

14.3. Labeling

Study intervention labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All study intervention must be stored at controlled temperatures. Guidance on storage temperature is provided in the Site Investigational Product Procedures Manual.

Vials must be stored in a secured location with no access for unauthorized personnel. All study product storage equipment (including refrigerators, freezers) must be equipped with a continuous temperature monitor and alarm, and with back-up power systems. In the event that study intervention is exposed to temperatures outside the specified temperature ranges, all relevant data will be sent to the sponsor to determine if the affected study intervention can be used or will be replaced. The affected study intervention must be quarantined and not used until further instruction from the sponsor is received.

A pharmacist/qualified staff member will prepare all doses for vaccine administration and provide it for dispensing. In the main study, blinding will be achieved by preparation of study intervention by unblinded qualified study-site personnel not involved in any other study-related procedures, and by the administration of study intervention in a masked syringe in a way that maintains double-blinding. In the extension phase, the preparation of the study intervention will be unblinded.

Full details on the preparation, the holding time and storage conditions from the time of preparation to delivery of Ad26.ZEBOV and MVA-BN-Filo and active control are provided in the Site Investigational Product Procedures Manual and Site Blinding Plan.

14.5. Intervention Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention will be documented on the Investigational Product Destruction Form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the Investigational Product Destruction Form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to study participants. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure and Addendum (if applicable) for Ad26.ZEBOV and MVA-BN-Filo
- Site Investigational Product Procedures Manual and Site Blinding Plan
- Laboratory manual
- IWRS Manual
- Electronic Data Capture (eDC) Manual/electronic CRF Completion Guidelines
- Sample ICF
- Participant diaries
- TOU
- Rulers, thermometers
- Participant wallet card

16. ETHICAL ASPECTS

16.1. Study-specific Design Considerations

Parent(s)/guardian of potential participants will be fully informed of the risks and requirements of the study and, during the study, they will be given any new information that may affect their decision to continue participation of their child. They will be told that their consent for their child to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only parent(s)/guardian of participants who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be allowed to enroll their child.

The primary ethical concern is the safety of the enrolled infants.

When referring to the signing of the ICF, the terms guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in

research. For each participant, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. For the purposes of this study, all references to participants who have provided consent refers to the participant and his or her parent(s) or the participant's guardian(s) or legally acceptable representative(s) who have provided consent according to this process.

The results of the study may be made available to the parent(s)/guardian of the participant at the conclusion of the study according to local standards/restrictions.

Test of Understanding

The TOU (see Appendix 1) is a short assessment of the parent(s)/guardian of the potential participant's understanding of key aspects of the study. The test will help the study staff to determine how well the parent(s)/guardian understand the study and their requirements for participation of their child.

The parent(s)/guardian must pass the TOU, indicating that he or she understands the purpose of, and procedures required for the study, after reading the informed consent and after the investigator or designee has provided detailed information on the study and has answered the questions of the parent(s)/guardian. The parent(s)/guardian must subsequently sign the ICF, indicating that he or she is willing to allow their child to participate in the study.

Parent(s)/guardians are allowed to retake the test twice to achieve the passing score (≥90%) required for participation of their child in the study. If a parent/guardian fails to achieve the passing score, further information and counseling will be provided by the study team member.

Any parent/guardian of a potential participant not capable of understanding the key aspects of the study, and their requirements for participation, should not be allowed to enroll their child.

Blood volume

The total blood volume to be collected in the main study is expected to be 8.0-9.5 mL, and 2 mL in the extension phase. Details are provided in the Time and Events Schedule. The study-related blood volumes obtained (including any losses during phlebotomy) will not exceed 3% of the total blood volume during a period of 4 weeks and will not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90 mL/kg body weight; 3% is 2.4 mL blood per kg body weight.[9] The allowable blood volume calculations are based on the 10th percentile for growth charts for infants.[21]

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)

- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

The parent(s)/guardian of a participant (in this section referred to as the legally acceptable representative) must give written consent according to local requirements after the nature of the study (main study and extension phase [if applicable]) has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the legally acceptable representative can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to the legally acceptable representative of potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. The legally acceptable representative will be informed that the participation of their child is voluntary and that they may withdraw consent to participate at any time. They will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the legally acceptable

representative agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations.

The legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the legally acceptable representative is obtained.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the legally acceptable representative includes explicit consent for the processing of personal data of the participant and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The legally acceptable representative has the right to request through the investigator access to the personal data of their child and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand Ad26.ZEBOV and MVA-BN-

Filo, to understand EVD, to understand differential intervention responders, and to develop tests/assays related to Ad26.ZEBOV and MVA-BN-Filo and EVD. The research may begin at any time during the study or the post-study storage period.

Parent(s)/guardian will be asked to consent voluntarily for their child's blood samples to be stored for other research studies that may be done after this study is completed. Participants for whom such consent is not given, can participate in the immunogenicity assessments without having their blood samples stored for future testing (see also Section 10.2). In such case, their blood samples will be destroyed after all the immunogenicity tests have been concluded (as agreed by the sponsor).

All samples, for which consent has been obtained and for which additional material is available after study-specified testing is complete, will be stored for future testing. A PCR test may be performed to test for presence of Ebola virus in the samples if samples need to be exported. Applicable approvals will be sought before any such samples are used for analysis not specified in the protocol or a protocol amendment approved by the IEC/IRB.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Parent(s)/guardian may withdraw consent for their child's samples to be stored for research.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

17.2. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the

change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.3. Regulatory Documentation

17.3.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.3.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement

- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.4. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by participant identification and age at initial informed consent. In cases where the subject is not randomized into the study, the date seen and age at initial informed consent will be used.

The investigator must also complete a participant screening log, which reports on all participants who were seen to determine eligibility for inclusion in the main study and separately for the extension phase of the study.

17.5. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The participant's diary used to collect information regarding solicited symptoms after vaccination will be considered source data.

The following data will be recorded directly into the CRF and will be considered source data:

- Race
- Pulse/heart rate and respiratory rate
- Body length and weight
- Details of physical examination

17.6. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.7. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or

designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.8. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.9. Monitoring

The sponsor will perform study site visits to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the vaccination unit and/or clinic records (source documents) (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the

relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In the main study, there will be independent monitoring of the pharmacy and preparation of study intervention by an unblinded monitor (independent study intervention monitor); regular monitors will be blinded. In the extension phase, the preparation of the study intervention will be unblinded.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

17.10. Study Completion/Termination

17.10.1. Study Completion/End of Study

The study is considered completed at final database lock, which will occur after the last participant in the study has completed their last study-related visit, or left the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.10.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study intervention development

17.11. On-site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for

consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.12. Use of Information and Publication

All information, including but not limited to information regarding Ad26.ZEBOV and MVA-BN-Filo or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of Ad26.ZEBOV and MVA-BN-Filo, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or

regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

18. COVID-19 APPENDIX: GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID 19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

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Appendix 1: Test of Understanding

MAIN STUDY

Note: A culturally appropriate translation will be made available to the parent(s)/guardian of the participants.

Please read each question and answer whether the statement is **True** or **False**.

True ☐	False ☐	1. The vaccines your baby will receive in this study will definitely protect against Ebola.
True ☐	False ☐	2. You will need to bring your baby to the clinic for 9 visits during the entire study period.
True ☐	False ☐	3. The vaccines in this study can give your baby Ebola disease.
True ☐	False ☐	4. One purpose of this study is to determine if these vaccines are safe to administer to babies.
True ☐	False ☐	5. You will need to avoid engaging your baby in activities that may expose him/her to Ebola virus.
True ☐	False ☐	6. Your baby may not be given the same vaccines as the other babies in this study.
True ☐	False ☐	7. You may withdraw your baby from the study at any time if you choose.
True ☐	False ☐	8. A baby participating in this study may experience side effects after vaccination.
True ☐	False ☐	9. The clinical staff are allowed to share information about your baby with other people not involved in the study.
True ☐	False ☐	10. You will be paid some monies for allowing your baby to participate in this study.

EXTENSION PHASE

Note: A culturally appropriate translation will be made available to the parent(s)/guardian of the participants.

Please read each question and answer whether the statement is **True** or **False**.

True	False	
☐	☐	1. The vaccines your child will receive in this second period of the study will definitely protect against Ebola.
☐	☐	2. You will need to bring your child to the clinic for 7 visits during this study period.
☐	☐	3. The vaccines in this study can give your child Ebola disease.
☐	☐	4. One purpose of this study is to determine if these vaccines are safe to administer to children.
☐	☐	5. You will need to avoid engaging your child in activities that may expose him/her to Ebola virus.
☐	☐	6. Your child will be given the same vaccines as in the first period of this study.
☐	☐	7. You may withdraw your child from the study at any time if you choose.
☐	☐	8. A child participating in this study may experience side effects after vaccination.
☐	☐	9. The clinical staff are allowed to share information about your child with other people not involved in the study.
☐	☐	10. You will be paid some monies for allowing your child to participate in this study.

Appendix 2: Toxicity Grading Scale for Healthy Pediatric Participants up to 3 Years of Age Enrolled in Preventive Vaccine Clinical Trials

Adapted from: Division of Microbiology and Infectious Diseases (DMID° Pediatric Toxicity Tables (November 2007, draft). For adverse events not included in the tables below, refer to the severity criteria guidelines in Section 12.1.3. Local lab references take preference over the DMD table and the different grades.

The abbreviations used in the following tables are: LLN: lower limit of normal; IV: intravenous; ULN: upper limit of normal.

LOCAL REACTIONS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Tenderness	Mild discomfort to touch; minimal to no limitation of use of limb	Notable discomfort to touch; Greater than minimal limitation of use of limb	Significant discomfort at rest; Severe limitation of use of limb	Hospitalization or ER visit for treatment
Erythema	<10 mm	10 25 mm	26 50 mm	>50 mm or any grade 3 with hospitalization or ER visit for treatment
Swelling	<10 mm	10 25 mm	26 50 mm	>50 mm or any grade 3 with hospitalization or ER visit for treatment

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin for children greater than 3 months and less than 2 years of age	**9.0-9.9 gm/dL**	**7.0-8.9 gm/dL**	**<7.0 gm/dL**	**Cardiac Failure secondary to Anemia**
Hemoglobin for children greater than 2 years of age	10.0 10.9 gm/dL	7.0 9.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to Anemia
Absolute Neutrophil Count	**750-1200/mm^3**	**400-749/mm^3**	**250-399/mm^3**	**<250/mm^3**
Platelets	75,000 99,999/mm^3	50,000 74,999/mm^3	25,000 49,999/mm^3	<25,000/mm^3
Prothrombin Time (PT)	1.1 1.2 x ULN	1.3 1.5 x ULN	1.6 3.0 x ULN	>3.0 x ULN
Partial Thromboplastin Time (PTT)	1.1 1.6 x ULN	1.7 2.3 x ULN	2.4 3.0 x ULN	>3.0 x ULN

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bilirubin (Fractionated bilirubin test must be performed when total bilirubin is elevated)				
Bilirubin for children greater than 3 months of age (when accompanied by any increase in other liver function test)	1.1 <1.25 x ULN	1.25 <1.5 x ULN	1.5 1.75 x ULN	>1.75 x ULN
Bilirubin for children greater than 3 months of age (when other liver functions are in the normal range)	1.1 <1.5 x ULN	1.5 <2.0 x ULN	2.0 3.0 x ULN	>3.0 x ULN
AST (SGOT)	1.1 <2.0 x ULN	2.0 <3.0 x ULN	3.0 8.0 x ULN	>8.0 x ULN
ALT (SGPT)	1.1 <2.0 x ULN	2.0 <3.0 x ULN	3.0 8.0 x ULN	>8.0 x ULN
GGT	1.1 <2.0 x ULN	2.0 <3.0 x ULN	3.0 8.0 x ULN	>8.0 x ULN
Pancreatic Amylase	1.1 1.4 x ULN	1.5 1.9 x ULN	2.0 3.0 x ULN	>3.0 x ULN
Uric Acid	7.5 9.9 mg/dL	10.0 12.4 mg/dL	12.5 15.0 mg/dL	>15.0 mg/dL
Loss of Appetite	Feeding minimally reduced	Feeding reduced by more than 50% of normal for the child	Refusing all feeds	No solid or liquid taken orally for in the last 24 hours; requires intravenous fluids
Diarrhea	Change in consistency of stools OR increase of 1 3 stools over baseline per 24 hour period	liquid/watery stools OR increase of 4 to 6 stools over baseline per 24 hour period	Increase of ≥7 stools over baseline per 24 hour period	Requires IV fluid resuscitation and electrolytes repletion OR hypotensive shock
Constipation	Slight change in consistency and/or frequency of stools	Hard, dry stools with a change in frequency	Intestinal obstruction accompanied with abdominal pain	Hospitalization; Severe abdominal distention and vomiting accompanied with severe abdominal pain
Vomiting	1 episode/ day (24h)	2 3 episodes per day (24h)	4 6 episodes per day (24h)	Greater than 6 episodes per day (24h) OR intractable vomiting

ELECTROLYTES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine				
3 Months – 2 Years of age	0.6 0.8 x ULN	0.9 1.1 x ULN	1.2 1.5 x ULN	> 1.5 x ULN
2 Years – 3 Years of age	0.7 1.0 x ULN	1.1 1.6 x ULN	1.7 2.0 x ULN	>2.0 x ULN
Hypernatremia		145 149 mEq/L	150 155 mEq/L	>155 mEq/L or abnormal sodium AND mental status changes
Hyponatremia		130 135 mEq/L	129 124 mEq/L	<124 mEq/L or abnormal sodium AND mental status changes
Hyperkalemia	5.0 5.9 mEq/L	6.0 6.4 mEq/L	6.5 7.0 mEq/L	>7.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypokalemia	3.0 3.5 mEq/L	2.5 2.9 mEq/L	2.0 2.4 mEq/L	<2.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypercalcemia	10.5 11.2 mg/dL	11.3 11.9 mg/dL	12.0 12.9 mg/dL	>13.0 mg/dL
Hypocalcemia	7.8 8.4 mg/dL	7.0 7.7 mg/dL	6.0 6.9 mg/dL	>6.0 mg/dL
Hypomagnesemia	1.2 1.4 mEq/L	0.9 1.1 mEq/L	0.6 0.8 mEq/L	<0.6 mEq/L or abnormal magnesium AND cardiac arrhythmia
hypoglycemia	55 65 mg/dL	40 54 mg/dL	30 39 mg/dL	<30 mg/dL or adnormal glucose AND mental status changes
Hyperglycemia	116 159 mg/dL	160 249 mg/dL	250 400 mg/dL	>400 mg/dL or ketoacidosis
Proteinuria	Tr 1+ or <150 mg/day	2+ or 150 499 mg/day	3+ or 500 1000 mg/day	4+ or Nephrotic syndrome >1000 mg/day
Hematuria	Microscopic <25 cells/hpf	Microscopic >25 cells/hpf	Gross hematuria	Hospitalization; Life threatening consequences

Neurologic				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Irritability	Easily consolable; minimal or no interference with activity. Episodes of continuous crying <60 min.	Difficult to console. Episodes of continuous crying >60 min <120 min	Inconsolable, prevents daily activity. Episodes of continuous crying >120 min	Hospitalization or ER visit for treatment
Decreased Activity	Minimal decrease in alertness, minimal or no interference with activity	Some interference with activity, slightly subdued	unable to achieve normal level of alertness, lethargic	ER visit or hospitalization for treatment or life threatening consequences
Neuropathy/ Lower Motor Neuropathy		Mild transient Paresthesia only	Persistent or progressive paresthesia, burning sensation in feet, or mild dysesthesia; no weakness; mild to moderate deep tendon reflex changes; no sensory loss	Onset of significant weakness, decrease or loss of DTRs, sensory loss in "stocking glove" distribution, radicular sensory loss, multiple cranial nerve involvement; bladder or bowel dysfunction, fasciculations, respiratory embarrassment from chest wall weakness.
Myopathy or Neuromuscular Junction Impairment	Normal or mild (<2 x ULN) CPK elevation	Mild proximal weakness and/or atrophy not affecting gross motor function. Mild myalgias, +/ mild CPK elevation (<2 x ULN)	Proximal muscle weakness and/or atrophy affecting motor function +/ CPK elevation; or severe myalgias with CPK >2 x ULN;	Onset of myasthenia like symptoms (fatigable weakness with external, variable ophthalmoplegia and/or ptosis), or neuromuscular junction blockade (acute paralysis) symptoms
OTHER				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Fever/pyrexia	38.0 38.4 °C or 100.4 101.1 °F	38.5 38.9 °C or 101.2 102.0 °F	39.0 40.0 °C or 102.1 104.0 °F	Greater than 40 °C or 104.0 °F
Acute allergic reaction	Pruritus without Rash	Pruritic Rash	Mild Urticaria	Severe Urticaria Anaphylaxis, Angioedema
Stomatitis	Mild discomfort	Painful, difficulty swallowing, but able to eat and drink	Painful: unable to swallow solids	Painful: unable to swallow liquids; requires IV fluids
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Hospitalization

Appendix 3: Thrombotic Events to be Reported

At the time of protocol amendment 4 writing, the list of thrombotic events to be reported to the sponsor as potential TTS is provided below. Further guidance may become available on thrombotic events of interest.

- MedDRA PTs for large vessel thrombosis and embolism

  Aortic embolus, aortic thrombosis, aseptic cavernous sinus thrombosis, brain stem embolism, brain stem thrombosis, carotid arterial embolus, carotid artery thrombosis, cavernous sinus thrombosis, cerebral artery thrombosis, cerebral venous sinus thrombosis, cerebral venous thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis, mesenteric artery embolism, mesenteric artery thrombosis, mesenteric vein thrombosis, splenic artery thrombosis, splenic embolism, splenic thrombosis, thrombosis mesenteric vessel, visceral venous thrombosis, hepatic artery embolism, hepatic artery thrombosis, hepatic vein embolism, hepatic vein thrombosis, portal vein embolism, portal vein thrombosis, portosplenomesenteric venous thrombosis, splenic vein thrombosis, spontaneous heparin-induced thrombocytopenia syndrome, femoral artery embolism, iliac artery embolism, jugular vein embolism, jugular vein thrombosis, subclavian artery embolism, subclavian vein thrombosis, obstetrical pulmonary embolism, pulmonary artery thrombosis, pulmonary thrombosis, pulmonary venous thrombosis, renal artery thrombosis, renal embolism, renal vein embolism, renal vein thrombosis, brachiocephalic vein thrombosis, vena cava embolism, vena cava thrombosis, truncus coeliacus thrombosis

- MedDRA PTs for more common thrombotic events

  Axillary vein thrombosis, deep vein thrombosis, pulmonary embolism, MedDRA PTs for acute myocardial infarction*, MedDRA PTs for stroke*

Source: Shimabukuro T. CDC COVID-19 Vaccine Task Force. Thrombosis with thrombocytopenia syndrome (TTS) following Janssen COVID-19 vaccine. Advisory Committee on Immunization Practices (ACIP). April 23, 2021. https://www.cdc.gov/vaccines/acip/meetings/slides-2021-04-23.html.

*Vaccine Adverse Event Reporting System (VAERS) Standard Operating Procedures for COVID-19 (as of 29 January 2021) https://www.cdc.gov/vaccinesafety/pdf/VAERS-v2-SOP.pdf

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Vaccines & Prevention, B.V.

Signature: [electronic signature appended at the end of the protocol] Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	30-Sep-2021 12:04:18 (GMT)	Document Approval