VAC52150EBL2011

An open label study to evaluate the safety and immunogenicity of an Ad26.ZEBOV booster dose in children previously vaccinated with the Ad26.ZEBOV and MVA-BN-Filo vaccine regimen

Protocol VAC52150EBL2011; Phase 2

Innovative Medicines Initiative

London School of Hygiene and Tropical Medicine and
and Janssen Vaccines and Prevention B.V.

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

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This study will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice guidelines, protocol and all applicable local regulations.

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ABBREVIATIONS

Ad26.ZEBOV	adenovirus serotype 26 expressing the Ebola virus Mayinga glycoprotein
AE	adverse event
CRF	case report form
DMID	Division of Microbiology and Infectious Diseases
EBOV	Ebola virus
eDC	electronic data capture
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EPI	Expanded Program on Immunisation
EVD	Ebola virus disease
FANG	Filovirus Animal Non-Clinical Group
GCP	Good Clinical Practice
GP	glycoprotein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IM	intramuscular
LLOQ	lower limit of quantitation
LSHTM	London School of Hygiene & Tropical Medicine
MedDRA	Medical Dictionary for Regulatory Activities
mL	millilitres
MVA-BN-Filo	Modified Vaccinia Ankara Bavarian Nordic vector expressing multiple filovirus proteins
PCR	polymerase chain reaction
PI	Principal Investigator
PQC	Product Quality Complaint
RBC	red blood cell
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
TOU	Test of Understanding
VISP	vaccine induced seropositivity
vp	viral particle(s)
WBC	white blood cell
WHO	World Health Organisation

PROTOCOL AMENDMENTS

Protocol Versions	DATE
Original Protocol, Version 1.0	30/10/2020
Amendment 1, Protocol Version 2.0	15/06/2021

Amendments below are listed beginning with the most recent amendment.

Amendment 1 (This document)
The overall reasons for the amendment:

- To include the assessment of neutralising antibody responses directed against the Ad26 vector before booster vaccination as an exploratory outcome of the study.
- To add safety information on the Ad26-based vaccines, following the latest update of the Investigator's Brochure and Addendum.
- To add Adverse Events of Special Interest

The changes made to the clinical protocol VAC52150EBL2011 are listed below, including the rationale of each change and a list of all applicable sections.

Rationale: the assessment of neutralising antibody responses directed against the Ad26 vector will be useful to understand if previous immunity against the Ad26 vector influences the immune response to the Ad26.ZEBOV booster. The assessment of neutralising antibody responses directed against the Ad26 vector before booster vaccination has been included as an exploratory outcome of the study.

SYNOPSIS
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Rationale: new information on the safety of the Ad26-based vaccines, in particular, the risk of thrombosis with thrombocytopenia syndrome (TTS), has been included following the latest update of the Investigator's Brochure Addendum.

Clinical Safety Experience with Ad26-based Vaccines in section 1.2.3 Potential Risks

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Rationale: history of thrombotic thrombocytopaenia syndrome (TTS) or heparin-induced thrombocytopaenia and thrombosis (HITT) have been mentioned as conditions that would increase the risk of an adverse outcome from participation in the study in exclusion criterion 10.

4.2 EXCLUSION CRITERIA

Rationale: Thrombotic events and symptomatic thrombocytopenia have been added to the protocol as Adverse Events of Special Interest.

Adverse Events of Special Interest in section 11.1.1 Adverse Event Definitions and Classifications APPENDIX 2

Rationale: inconsistent information about retesting of values, rescreening and rescheduling of the vaccination (Day 1) have been corrected.

8.1.3 Vaccination Period

Rationale: Minor editorial changes have been made.

Throughout the document

Rationale: References have been updated.

REFERENCES

SYNOPSIS

TITLE

An open label study to evaluate the safety and immunogenicity of an Ad26.ZEBOV booster dose in children previously vaccinated with the Ad26.ZEBOV and MVA-BN-Filo vaccine regimen.

RATIONALE

Over 600 children have received the adenovirus serotype 26 expressing the Ebola virus Mayinga glycoprotein (Ad26.ZEBOV), modified Vaccinia Ankara Bavarian Nordic vector expressing multiple filovirus proteins (MVA-BN-Filo) Ebola vaccine regimen in the EBL2002 and EBL3001 clinical trials. The vaccine regimen was well-tolerated and highly immunogenic in children; however, the durability of vaccine-induced immune responses is not known. In adults previously vaccinated with the Ad26.ZEBOV and MVA-BN-Filo regimen, a booster vaccination with Ad26.ZEBOV was safe and induced a strong anamnestic response within seven days of the booster vaccination. It is important to establish if a booster dose of Ad26.ZEBOV is safe and immunogenic also in children, as this can guide the clinical use of the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen in this age group. For example, it could support the strategy of boosting immunised children at the start of an Ebola outbreak.

STUDY OBJECTIVES AND HYPOTHESIS

This study aims to evaluate the safety and immunogenicity of an Ad26.ZEBOV booster dose in healthy children who were previously (>2 years) vaccinated with the Ad26.ZEBOV (dose 1) followed by MVA-BN-Filo (dose 2) 56 days later, by monitoring adverse events (AEs) following the booster vaccination and by assessing binding antibody responses using the Filovirus Animal Non-Clinical Group (FANG) Enzyme-Linked Immunosorbent Assay (ELISA).

Primary Objectives

- To assess the safety and tolerability of a booster dose of Ad26.ZEBOV at a dose of $5x10^{10}$ viral particles (vp) in children previously vaccinated with the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen with a 56-day interval.

- To assess vaccine-induced humoral immune responses to the Ebola virus glycoprotein (EBOV GP), as measured by FANG ELISA, at 7 and 21 days following a booster dose of Ad26.ZEBOV at a dose of $5x10^{10}$ vp in children previously vaccinated with the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen with a 56-day interval.

Exploratory Objectives

- To assess neutralising antibody responses directed against the Ad26 vector before booster vaccination as measured by a virus neutralization assay (VNA).

Hypothesis

As this study is designed to provide descriptive information regarding safety and immunogenicity without formal treatment comparisons, no formal statistical hypothesis testing is planned.

OVERVIEW OF STUDY DESIGN

This is an open-label study evaluating the immune response to a booster dose of Ad26.ZEBOV administered to children who were previously vaccinated with Ad26.ZEBOV followed by MVA-BN-Filo 56 days later. Only subjects who received the Ad26.ZEBOV and MVA-BN-Filo regimen during their participation in the

VAC52150EBL3001 (EBOVAC-Salone) vaccine trial are eligible for enrolment in this study. Participants will be recruited in two age groups: children aged 4-11 years at the time of dose 1 vaccination and children aged 1-3 years at the time of dose 1 vaccination in the EBOVAC-Salone trial. Approximately 25 subjects will be enrolled in each of these two age groups.

Parents/guardians will be asked to consent for the participation of their children in the study. Children aged 7 years and older at the time of enrolment in this study will be asked to give positive assent for their participation. Participants will be followed up to 28 days after their booster vaccination.

The Principal Investigator, together with the sponsor's medical safety officer, will be responsible for the safety monitoring of the study.

The study will be conducted in Kambia, Sierra Leone.

SUBJECT POPULATION

Potential participants must be healthy children (based on physical examination, medical history, a haematological assessment and clinical judgment) who received the Ad26.ZEBOV and MVA-BN-Filo vaccine regimen in the EBOVAC-Salone trial and were aged ≥1 to ≤11 years at the time of dose 1 vaccination. They must also be enrolled in the long-term follow-up study to the EBOVAC-Salone trial, VAC52150EBL3005 (EBOVAC-Salone Extension study) but not in the immunogenicity subset.

DOSAGE AND ADMINISTRATION

A single dose of Ad26.ZEBOV at a dose of $5x10^{10}$ vp administered intramuscularly.

SAFETY EVALUATIONS

Solicited local (at the administration site) and systemic AEs will be assessed on the day of vaccination and using a diary for a period of seven days following the booster vaccination. Unsolicited AEs will be tracked for 28 days following booster vaccination, while serious adverse events will be tracked for the duration of the study.

IMMUNOGENICITY EVALUATIONS

Blood will be drawn for assessments of immune responses at the time points indicated in the TIME AND EVENTS SCHEDULE. The site staff will perform sample collection and processing according to current versions of approved standard operating procedures.

Future scientific research may be conducted to further investigate Ebola vaccine- and disease-related questions and to study other infections of public health importance in Sierra Leone and neighbouring countries. This may include the development of new, or the improvement of, existing techniques to characterize EBOV-directed immune responses or diagnostic tests. No additional samples will be taken for these analyses, however, residual samples from the study tests may be retained for these purposes and analysed after the end of the study.

STATISTICAL METHODS

The primary analysis will be done when all subjects have completed their 28-day post-booster visit or discontinued earlier. This analysis will include all available data up to this point.

Sample Size Determination

The sample size is a convenience sample and is not based on formal hypothesis testing considerations.

SAFETY ANALYSES

No formal statistical testing of safety data is planned. Safety data will be analysed descriptively by age group, 1-3 years and 4-11 years (age the participant was when they received dose 1 vaccination in the EBOVAC-Salone trial).

IMMUNOGENICITY ANALYSES

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (i.e. geometric mean and 95% confidence interval, as appropriate) will be calculated for continuous immunologic parameters at all available time points (i.e. Day 1, 8 and 22). Graphical representations of immunologic parameters will be made as applicable.

Frequency tabulations will be calculated for discrete (qualitative) immunologic parameters (i.e. responder rate), as applicable. Responders rate defined as >2.5-time increase over baseline value (or lower limit of quantitation [LLOQ]) pre-dose 1 vaccination in the EBOVAC-Salone trial, will be calculated depending on availability of sample results from the EBOVAC-Salone trial.

TIME AND EVENTS SCHEDULE

Study Procedures	Screening (≤28 days)[a]	Study Period				
		Day 1 Booster	Days 2-7	Day 8 (+ 3 days)	Day 22 (± 3 days)	Day 29[b] (± 3 days)
Test of Understanding (TOU)[c]	X					
Informed consent and assent (if applicable) [d]	X					
Medical history and demographics	X					
Inclusion/exclusion criteria[e]	X	X				
Urine pregnancy test[f]	X	X[g]				
Physical examination[h]	X	X[f]		X	X	X[b]
Vital signs [i]	X	X		X	X	X[b]
Vaccine Administration[d]		X				
30 minutes post-vaccination observation [j]		X				
Distribution of participant diary		X				
Completion of the diary at home[k]		X	X			
Completion and review of the diary by study site personnel				X		
Solicited adverse events recording [j]		X	X	X		
Unsolicited adverse events recording		From booster vaccination (Day 1) onwards until 28 days post booster				
Serious Adverse Events [l]	Continuous					
Concomitant medications [m]	X	X	X	X	X	X
Blood draw						
Haematology (i.e. full blood count)	X			X	X	
Immunogenicity (serum) [n]		X		X	X	
Approximate blood draw volumes						
Haematology: 2.0 mL per blood draw	2.0			2.0	2.0	
Immunogenicity: Participants aged<6 years, 2.5 mL per blood draw Particpcant aged 6 years and older, 5.0 mL per blood draw		2.5 5.0		2.5 5.0	2.5 5.0	
Total (Haematology + Immunogenicity) Participants aged **<6 years** Participant aged **6 years and older**	**2.0** **2.0**	**2.5** **5.0**		**4.5** **7.0**	**4.5** **7.0**	

NOTE: In case of early withdrawal due to an adverse event (AE), the investigator or clinical designee will collect all information relevant to the AE and safety of the participant, and will follow the participant until resolution of the AE or until reaching a clinically stable endpoint. Parents/guardians who withdraw consent, or participants who wish to withdraw assent, will be offered an optional visit for safety follow-up (before the formal withdrawal of consent). Participants and/or parents/guardians have the right to refuse such a visit for themselves/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 of the 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 Day 29 visit can be conducted via phone call if the participant is unable, or does not wish, to attend the clinic for this visit. If Day 29 visit is conducted over the phone, no physical exam and no vital signs will be collected or recorded for this visit.

[c] 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.

[d] Informed consent must be obtained before any study-related activities are performed.

[e] The investigators should ensure that all study enrollment criteria have been met at the end of the enrolment period and before the booster 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 participating in the study.

[f] For all adolescent girls who are ≥12 years of age at the time of screening.

[g] Prior to study vaccine administration.

[h] A full physical examination including also body weight and height will be conducted at screening. At following vists, a brief physical examination will be symptom-directed. Physical examination findings (i.e. abnormalities) prior to vaccination are to be recorded as medical history, after vaccination as adverse event(s).

[i] Vital signs include blood pressure, pulse/heart rate (at rest), respiratory rate, and body temperature.

[j] After the 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 (at the injection site) and systemic adverse events and unsolicited adverse events emerging during the observation period will be recorded in the CRF.

[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/guardian, to document symptoms of solicited local (at the injection site) and systemic adverse events in the evening after the vaccination and then daily for the next 6 days at approximately the same time each day. Day 8 of the diary will be completed at the study clinic by a study doctor or nurse.

[l] Serious adverse events and/or special reporting situations that are related to study procedures 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 vaccination onwards until the end of the study.

[m]Concomitant therapies must be recorded from screening onwards until 28 days post-vaccination.

[n]Serum aliquots for FANG ELISA at all timepoints (D1, D8, D22). Serum aliquot for Ad26 VNA testing at D1.

1 INTRODUCTION

Ebola viruses belong to the Filoviridae family and cause Ebola virus disease (EVD), which can induce severe haemorrhagic fever in humans and nonhuman primates. Case fatality rates in EVD range from 25% to 90% (average: 50%) according to the World Health Organisation (WHO). [1]

Janssen Vaccines & Prevention B.V., in collaboration with Bavarian Nordic GmbH Denmark and in conjunction with an Innovative Medicines Initiative consortium led by 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 Oxford and the Sierra Leone College of Medicine and Allied Health Sciences as partners, is investigating the potential of a prophylactic Ebola vaccine regimen (VAC52150) comprised of the following two candidate vaccines:

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

MVA-mBN226B, further referred to as MVA-BN-Filo, is a non-replicating multivalent vaccine expressing the Sudan virus GP, the EBOV GP, the Marburg virus Musoke GP, and the Tai Forest virus (formerly known as *Côte d'Ivoire ebolavirus*) nucleoprotein, and is produced in chicken embryo fibroblast cells. The EBOV GP expressed by MVA-BN-Filo has 100% homology to the one expressed by Ad26.ZEBOV.

The GP of the Ebola virus (EBOV) responsible for the 2013-2016 epidemic in West Africa had 97% homology to the EBOV GP used in this vaccine regimen.

For the most up-to-date nonclinical and clinical information regarding Ad26.ZEBOV and MVA-BN-Filo, please refer to the latest versions of the Investigator's Brochures (IBs) and Addenda (if applicable) [2, 3]. A brief summary of the nonclinical and clinical information available at the time of the protocol writing is provided below.

1.1 BACKGROUND

The safety, reactogenicity, and immunogenicity of the Ad26.ZEBOV and MVA-BN-Filo vaccines have been evaluated in phase 1, 2 and 3 clinical trials. More than 100,000 participants, including children (1–17 years old) have received the Ad26.ZEBOV and MVA-BN-Filo vaccine regimen in a number of completed and ongoing clinical studies and in a large scale vaccination campaign in Rwanda. Data from these studies have shown that the two-dose heterologous Ad26.ZEBOV, MVA-BN-Filo vaccine regimen is generally well tolerated and able to induce humoral immune responses persisting for at least two years in adults and for at least one year in children.

Safety and immunogenicity of the Ad26.ZEBOV and MVA-BN-Filo vaccines in paediatric participants

In the VAC52150EBL2002 (Burkina Faso, Cote D'Ivoire, Uganda, Kenya) and VAC52150EBL3001 (Sierra Leone) studies, three age cohorts (12–17 years, 4–11 years and 1–3 years) were vaccinated with Ad26.ZEBOV or control followed by MVA-BN-Filo or control, 28 or 56 days later. The control used for Dose 1 and 2 in VAC52150EBL2002 was a placebo (i.e. saline injection). In VAC52150EBL3001, Dose 1 consisted of a meningococcal conjugate vaccine (MenACWY) and Dose 2 of placebo.

In these studies, the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen was well tolerated with no safety signals identified. Most solicited (local and systemic) AEs were mild to moderate. Overall, the frequency of grade 3 solicited AEs was low (<2%) in all children assigned to Ad26.ZEBOV, MVA-BN-Filo regimen. The most frequently reported solicited local AE was injection site pain; frequency was similar between the age cohorts, but higher in participants assigned to active vaccines than to placebo. The most frequently reported solicited systemic AEs was headache in the 12–17 years and 4–11 years age cohorts, and decreased appetite in the 1-3 years age cohort. The frequency of unsolicited AEs was higher in the 1-3 years age cohort compared to older children. The frequency of Grade 3 unsolicited AEs was similar across age cohorts. No serious adverse events (SAEs) were considered related to Ad26.ZEBOV or MVA-BN-Filo vaccines. The Ad26.ZEBOV, MVA-BN-

Filo vaccine regimen induced robust binding antibody responses, which persisted for at least up to 12 months. Younger children (1-3 years) had higher antibody responses compared to older children (4-11 years and 12-17 years age cohorts). [4, 5]

Safety and immunogenicity of an Ad26.ZEBOV booster dose in adult participants

An Ad26.ZEBOV booster vaccination was given to 29 adult participants, who were vaccinated approximately 2 years before with Ad26.ZEBOV followed by MVA-BN-Filo 56 days later in the VAC52150EBL3001 (EBOVAC-Salone) trial in Sierra Leone. The booster vaccination was safe and induced a strong anamnestic response in 96% of participants at seven days post-booster vaccination and in all 29 participants at 21 days post-booster vaccination. [6]

1.2 BENEFITS/RISKS OF PARTICIPATION

1.2.1 Potential Benefits

The 2-dose Ebola vaccine regimen (Ad26.ZEBOV followed by MVA-BN-Filo 56 days later) has received marketing authorisations for prophylactic use in adults and children ≥1 years old in the European Union.[7] The marketing authorisation also includes the possibility for an Ad26.ZEBOV booster dose to be given to subjects who received the 2-dose regimen more than 4 months earlier and are at imminent risk of infection with Ebola virus.[8] This vaccine regimen was previously shown to provide protection in vaccinated non-human primates against an EBOV challenge, which is fully lethal in unvaccinated control animals. Although clinical efficacy data are not available for this vaccine regimen, the marketing authorisation was granted on the basis of the potential clinical benefit induced by vaccination by correlating the magnitude of vaccine-elicited immune parameters in non-human primates with those observed in vaccinated humans in phase 1, 2 and 3 clinical studies.[9]

If the Ad26.ZEBOV booster dose is shown to be safe and immunogenic in children as in adults, the participants enrolled in this study may benefit from the potential protective benefit of the booster vaccination in the case of a future exposure to EBOV.

Participants will also benefit from clinical testing and physical examination; others may benefit from the knowledge that they may aid in the development of an Ebola vaccine.

1.2.2 Known Risks

Ad26.ZEBOV

The safety, reactogenicity, and immunogenicity of the Ad26.ZEBOV vaccine has been evaluated in a number of completed and ongoing clinical studies in adults and children. The vaccine was well tolerated, with no safety concerns identified. The vaccine mainly elicited some solicited local and systemic reactions, as expected with injectable vaccines, and there were no serious safety concerns in study participants. For details, see the safety data presented in Section 1.1. For the most up-to-date nonclinical and clinical information regarding Ad26.ZEBOV, refer to the latest versions of the IB and Addenda (if applicable) [2, 3].

1.2.3 Potential Risks

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

Risks Related to Vaccination

In general, intramuscular (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 the administration of a vaccine, including fever, chills, rash, nausea/vomiting, general itching, headache, myalagia, arthralgia, and fatigue.

Young children may also experience loss of appetite, diarrhoea, decreased activity/lethargy, and 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 vaccine. 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 15.1).

Concomitant Vaccination

Concomitant vaccination might have an influence on both the safety profile and immunogenicity of Ad26.ZEBOV. Likewise, the study intervention might have an influence on both the safety profile and immunogenicity of any concomitant vaccination. Therefore, a participant should not receive a live-attenuated vaccine from 30 days before the vaccination until 30 days after the 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 with the 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 (e.g., 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 (e.g., Expanded Program on Immunization [EPI] schedule according to the WHO regional office for West Africa).

Clinical Safety Experience with Ad26-based Vaccines

Thrombosis in combination with thrombocytopenia (thrombosis with thrombocytopenia syndrome [TTS]), in some cases accompanied by internal bleeding, has been observed very rarely following vaccination with the Janssen COVID-19 (Ad26.COV2.S) 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 approximately 1 to 2 weeks after vaccination, mostly in women under 60 years of age. Thrombosis in combination with thrombocytopenia can be fatal. The exact pathophysiology of TTS is unclear. This event has not been observed to date with any other Janssen Ad26-based vaccines. Participants should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, persistent abdominal pain, severe or persistent headaches, blurred vision, skin bruising or petechiae beyond the site of vaccination.

Vaccine Induced Seropositivity

The potential of a participant becoming polymerase chain reaction (PCR)-positive after vaccination was assessed in study VAC52150EBL1002. The risk for false positives is low and expected to decrease rapidly over time after administration of Ad26.ZEBOV.

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/guardians) will be informed.

1.2.3 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 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 medical reviewer evaluates all safety data (see Sections 3.1, 8.3, 10.7).

- 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. 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:

  - 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 (e.g. in case of grade 3 AEs). 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 AEs from the vaccination (Day 1) onwards until 28 days post-vaccination (Day 29). The investigator or clinical designee will document serious AEs and/or special reporting situations that are related to study procedures from the time a signed and dated informed consent form (ICF) is obtained onwards until the end of the study.

  - 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.

  - If acute illness (excluding minor illnesses such as diarrhoea or mild upper respiratory tract infection) or axillary temperature ≥38°C is present at the scheduled time for vaccination, the participant may be rescheduled for vaccination at a later time point within the window allowed for screening, or be withdrawn from vaccination at the discretion of the investigator and after consultation with the sponsor (see Section 6.1).

1.3 OVERALL RATIONALE FOR THE STUDY

Over 600 paediatric participants have received the Ad26.ZEBOV, MVA-BN-Filo Ebola vaccine regimen in the EBL2002 and EBL3001 clinical trials. [4, 5] The vaccine regimen was well-tolerated and highly immunogenic in children, however, the durability of the immune response is not known. In adults previously vaccinated with the Ad26.ZEBOV and MVA-BN-Filo regimen, an Ad26.ZEBOV booster vaccination was safe and induced a strong anamnestic response. [6] It is important to establish the safety and immunogenicity of a booster dose of Ad26.ZEBOV in children, as this can guide the clinical use of the vaccine regimen in this group. For example, it could support the strategy of boosting immunised children at the start of an Ebola outbreak.

2 OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1 OBJECTIVES AND ENDPOINTS

Primary Objectives

- To assess the safety and tolerability of a booster dose of Ad26.ZEBOV at a dose of $5x10^{10}$ viral particles (vp) in children previously vaccinated with the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen with a 56-day interval.

- To assess vaccine-induced humoral immune responses to the Ebola virus glycoprotein (EBOV GP), as measured by FANG ELISA, at 7 and 21 days following a booster dose of Ad26.ZEBOV at a dose of $5x10^{10}$ vp in children previously vaccinated with the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen with a 56-day interval.

Exploratory Objectives

- To assess neutralising antibody responses directed against the Ad26 vector before booster vaccination as measured by a virus neutralization assay (VNA).

2.2 HYPOTHESIS

As this study is designed to provide descriptive information regarding the safety and immunogenicity of a booster dose of Ad26.ZEBOV in children, no formal statistical hypothesis testing is planned.

3 STUDY DESIGN

3.1 OVERVIEW OF STUDY DESIGN

This is an open label phase 2 study evaluating the immune response to a booster dose of Ad26.ZEBOV administered to children who were previously vaccinated with Ad26.ZEBOV followed by MVA-BN-Filo 56 days later. Only subjects who received the Ad26.ZEBOV and MVA-BN-Filo regimen during their participation in the EBOVAC-Salone trial are eligible for enrolment in this study. Participants will be recruited in two age groups: children aged 4-11 years at the time of dose 1 vaccination and children aged 1-3 years at the time of dose 1 vaccination. Up to 25 subjects will be enrolled in each age group.

The study will consist of a screening period of up to 28 days, a booster vaccination (Day 1) and a post-booster vaccination follow-up period until 28 days post-vaccination (Day 29).

Parents/guardians will be asked to consent for the participation of their children in the study. Children aged 7 years and older at the time of enrolment in this study will be asked to give positive assent for their participation.

After informed consent and assent (if applicable) have been obtained, investigators should ensure that all study eligibility criteria have been met prior to the study vaccination on Day 1 (see list of inclusion and exclusion criteria in Section 4). Eligibility will be based on medical history, physical examinations (including body height and weight), vital sign measurements, a haematological (i.e. full blood count) assessment, and urine pregnancy test in all adolescent girls who are ≥12 years of age at the time of screening.

After vaccination, participants will remain under observation at the study site for at least 30 minutes for surveillance for any acute reactions, or longer if deemed necessary by the investigator. Following the vaccination, any unsolicited, solicited local or systemic AEs, 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 booster vaccination. Diaries will be completed at home by either a project field worker who will visit the participant or by the parent/guardian to document solicited local (at the injection site) and systemic AEs and body temperature, beginning on the evening of the vaccination, and then daily for the next 6 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, review, and complete the participant diary information at the 7-day post-vaccination visit (Day 8).

Unsolicited AEs will be recorded from the booster vaccination (Day 1) onwards until 28 days post-booster vaccination (Day 29). SAEs and/or special reporting situations that are related to study procedures will be reported from the time a signed and dated ICF is obtained onwards until the end of the study (Day 29).

Blood samples will be collected for immunogenicity assessments at Day 1 (i.e. the baseline sample before vaccination), 7 days post-vaccination (Day 8), and 21 days post-dose-vaccination (Day 22). At Day 8 and Day 22, a sample for haematology will also be collected.

Participants will exit the study after 28 days post-vaccination (Day 29). The study is considered completed at the site at final database lock, which will occur after the last participant has completed the last study visit or left the study.

4 PARTICIPANT POPULATION

The study will be open to healthy children (based on physical examination, medical history, a haematological assessment and clinical judgement) who received the Ad26.ZEBOV and MVA-BN-Filo vaccine regimen in the EBOVAC-Salone trial. The children must be enrolled in the long-term follow-up study to the EBOVAC-Salone trial, the VAC52150EBL3005 (EBOVAC-Salone Extension) study but not in the immunogenicity subset.

The inclusion and exclusion criteria for enrolling participants in this study are described in the following two subsections. If there is a question about the inclusion and exclusion criteria, 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 INCLUSION CRITERIA

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

1. Child must be enrolled in the VAC52150EBL3005 (EBOVAC-Salone Extension) study but not in the immunogenicity subset of EBOVAC-Salone Extension study.
2. Child must be a former participant in the VAC52150EBL3001 (EBOVAC-Salone) trial, and have received Ad26.ZEBOV (dose 1) vaccination followed by the MVA-BN-Filo (dose 2) vaccination within the EBOVAC-Salone trial window for dose 2 vaccination.
3. Child must have been aged 1 to 11 years old at the time of dose 1 vaccination in the EBOVAC-Salone trial.
4. The parent/guardian must consent for their child to participate in the VAC52150EBL2011 study by signing (or thumb printing, if illiterate) an ICF, indicating that he or she understands the purpose of, and procedures required for, the study, understands the potential risks and benefits of the study, and is willing to allow their child to participate in the study. If the parent/guardian cannot read or write, the procedures must be explained, and informed consent must be witnessed by a literate third party not involved in the conduct of the study. Children aged 7 years and older will be asked to give positive assent for their participation in the study and the assent procedure must be witnessed by an adult, literate parent/guardian/third party not involved in the conduct of the study, and documented.
5. The parent/guardian is willing/able to ensure that their child adheres to the prohibitions and restrictions specified in this protocol (see Section 4.3)

6. Child must be healthy in the investigator's clinical judgement (and the parent/guardian's judgement) on the basis of medical history, physical examination, vital signs, and a haematological assessment (i.e. full blood count) performed at screening. Subjects must meet the following haematology parameters within 28 days before Day 1:

    - Haemoglobin ≥8.0 g/dL for children aged 1 to <5 years, ≥9g/dL for children aged 5 or older
    - Platelet count ≥100 x 10^9/L
    - White blood cell count ≥5.0 x 10^9/L

    Note: The haematological assessment at screening is to be performed within 28 days prior to vaccination on Day 1 and may be repeated if it falls outside this time window.

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

7. Adolescent girls who have started their menstrual periods and/or are ≥12 years of age at the time of screening, must have a negative urine β-hCG pregnancy test at screening and immediately prior to the booster vaccination on Day 1.
8. The parent/guardian is available and willing to have their child participate for the duration of the study visits.
9. The parent/guardian must have the means to be contacted.
10. The parent/guardian must pass the Test of Understanding (TOU).

    Note: If the parent/guardian fails the TOU 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, he/she should not continue with enrolling or consenting procedures.

4.2 EXCLUSION CRITERIA

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

1. Participants in the EBOVAC-Salone trial who were allocated to the control arm receiving the WHO-prequalified Meningococcal Group A, C, W135 and Y conjugate vaccine.
2. Participants in the EBOVAC-Salone trial who were age 12 years and older at the time of dose 1 vaccination.
3. Known allergy or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine products (including any of the constituents of the study vaccine, e.g., polysorbate 80, ethylenediaminetetraacetic acid or L-histidine for Ad26.ZEBOV vaccine), including known allergy to chicken or egg proteins and aminoglycosides (gentamicin).
4. Presence of acute illness (this does not include minor illnesses such as mild diarrhoea or mild upper respiratory tract infection) or axillary temperature ≥38ºC on Day 1. Participants with such symptoms will be excluded from enrolment at that time but may be rescheduled for enrolment at a later date within the screening window.
5. Clinically significant history of skin disorder (e.g., 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.
6. Adolescent girls who are known to be pregnant or breastfeeding at screening.

7. Received a blood transfusion or other blood products within 8 weeks of vaccination day.

8. Children who have been vaccinated with live-attenuated vaccines within 30 days before the study vaccination, and with inactivated vaccine within 15 days before the study vaccination.

9. Children who, in the opinion of the investigator, are unlikely to adhere to the requirements of the study or are unlikely to complete the vaccination and observation

10. 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, e.g. history of thrombotic thrombocytopaenia syndrome (TTS) or heparin-induced thrombocytopaenia and thrombosis (HITT).

NOTE: Investigators should ensure that all study eligibility criteria have been met prior to the study vaccination on Day 1. If a subject's clinical status changes (including receipt of additional medical records or available laboratory results) after enrolment but before the vaccination (Day 1) so that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study.

4.3 PROHIBITIONS AND RESTRICTIONS

The parent/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 their parent/guardian must not travel to an area with an Ebola outbreak while the participant is enrolled in the study from the start of screening onwards until the last study visit. If applicable, any travelling to an area with an 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 child does not receive any experimental medication (including experimental vaccines other than the study intervention) as described in Section 7.

5 INTERVENTION ALLOCATION AND BLINDING

5.1 BLINDING

As this is an open-label study, blinding procedures are not applicable.

6 DOSAGE AND ADMINISTRATION

All participants will receive the Ad26.ZEBOV vaccine, at a concentration of $5x10^{10}$vp, as a 0.5 millilitres (mL) IM injection into the deltoid muscle.

Study intervention will be prepared by a pharmacist or qualified staff member with primary responsibility for study intervention preparation and dispensing of the vaccine.

Ad26.ZEBOV will be administered as a 0.5 mL IM injections in the deltoid muscle, by a study intervention administrator. The injection site should be free from any injury, local skin conditions, or other issue that might interfere with the evaluation of local reactions. No local or topical anaesthetic will be used prior to the injection.

Participants will remain at the site for at least 30 minutes after the vaccination for the detection of any acute reactions, or longer if deemed necessary by the investigator (e.g. in case of a grade 3 AEs). 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. The site 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 Procedure Manual specifies the procedures for administration of the study intervention.

Ad26.ZEBOV will be manufactured by Janssen Vaccines & Prevention B.V. and provided under the responsibility of the sponsor, LSHTM. Please refer to the IB for a list of excipients.

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:

- An acute illness at the time of vaccination (this does not include minor illnesses such as diarrhoea or mild upper respiratory tract infection).
- An axillary temperature ≥38°C at the time of vaccination.

Participants experiencing any of these events may be rescheduled for vaccination at a later time point within the window allowed for screening, or be withdrawn from vaccination at the discretion of the investigator and after consultation with the sponsor.

7 CONCOMITANT THERAPY

Concomitant therapies that the participant is taking at the time of screening must be recorded in the CRF at screening.

Should immunisation with an inactivated vaccine be required, it should be administered at least 15 days before or after administration of the 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 (e.g., rabies or tetanus), it must take priority over the study intervention. A participant will not postpone, forego, or delay the receipt of any recommended vaccine according to local schedules (e.g. EPI schedule according to the WHO regional office for West Africa).

Analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs may be used post-vaccination in case of medical need (e.g., 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-vaccination.

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.

8 STUDY EVALUATIONS

Prior to any study-related activities being performed, participants, or participant's parent/guardian, must have signed a study ICF (see Section 15.2.3 Consent)

8.1 STUDY PROCEDURES

8.1.1 Overview

The TIME AND EVENTS SCHEDULE summarises the frequency and timing of all study procedures, which 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 the 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 required windows.

Blood Sampling Volume

The approximate blood volumes collected in this study are indicated in the TIME AND EVENTS SCHEDULE. These study-related blood volumes obtained at each study visit (including any losses during phlebotomy) will not exceed 3% of the total blood volume. 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. [10] The allowable blood volume calculations are based on the 3rd percentile for growth charts for 1 to 5-year-old [11] and 6- to 10-year-old children. [12]

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

8.1.2 Screening Period

After signing and dating the ICF (see Section 16.2.3) and up to 28 days before Day 1 (day of vaccination), 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 participant and his/her parent/guardian will obtain written informed consent prior to study participation of the child.

After reading but before signing the ICF, the TOU will be administered to the parent/guardian. If the parent/guardian fails the TOU, they may repeat the test twice (and have to pass the third time for their child to be eligible) (for details, see Section 15.1).

The overall eligibility of the child to participate in the study will be assessed once all the screening results are available. Retesting of values (i.e. haematology) that lead to exclusion is allowed once using an unscheduled visit. If rescreening is required, all screening procedures (except TOU) should be repeated. Rescreening is allowed one time at the discretion of the study doctor. Study participants who qualify for inclusion will be contacted and scheduled for vaccination within 28 days.

A serum sample will be taken before vaccination at D1, to serve as a pre-vaccination baseline sample for immunogenicity assessments (see Section 8.4).

8.1.3 Vaccination Period

If eligible, the participant will be invited to come for the vaccination visit (Day 1). The investigator should ensure that all eligibility criteria have been met during the screening period. If a participant's clinical status changes (including available laboratory results or receipt of additional medical records) after screening but before the vaccination (Day 1) such that he/she no longer meets all eligibility criteria, then the participant should not be enrolled. Retesting of values and rescreening might be considered (see Section 8.1.2 for further information). Rescheduling of the vaccination (Day 1) visit, if the participant has an acute illness, is allowed within the screening window.

Before vaccination, a brief physical examination and measurement of vital signs will be performed.

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

Upon discharge from the site, the parent/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 the injection site) and systemic symptoms and will be trained on how to collect this information. Symptoms of solicited local and systemic AEs will be collected in the diary in the evening after the 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/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 7 days after the vaccination (Day 8) 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 AEs will be reported from the first day of vaccination until 28 days post-vaccination (Day 29).

SAEs and/or special reporting situations that are related to study procedures will be reported from the time a signed and dated ICF is obtained onwards until the end of the study (Day 29). All other SAEs and/or special reporting situations will be reported from the day of vaccination onwards until the end of the study (Day 29).

Participants will come to the site 7 and 21 days after the vaccination (Day 8 and Day 22) for safety and immunogenicity assessments. Please refer to 8.4 for details on the immunogenicity evaluations.

The parent/guardian will be instructed to contact the investigator anytime during the course of the study if their child experiences any AE or intercurrent illness that they perceive as relevant and/or can be possibly related to study intervention in their opinion.

When an enrolled participant completes or withdraws from the study, the investigator will complete an end-of-study form for the individual participant and provide a specific date for the end-of-study observation(s). When a participant withdraws before completing the study, the reason for withdrawal (if available) will be documented in the CRF and in the source documents.

Participants who appear to be lost to follow-up will be contacted, as per local practice, and the data recorded in the CRF. Participants lost to follow-up will have all data included for analysis.

8.2 PROCEDURES IN CASE OF A STUDY PAUSE

A study pause can affect participants that are awaiting the booster vaccination. After approval is granted to restart the study, participants who are awaiting the booster 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 8.1.2, excluding TOU). Participants that are rescreened due to a pause must have new safety assessments (including full blood count, physical examination, and vital signs) within 28 days of the booster 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 8.1.3).

8.3 SAFETY EVALUATIONS

8.3.1 Safety Assessments

The Principal Investigator, together with the Chief Investigator and the sponsor's medical safety officer or delegate, 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 8.3.2 have been met. Further safety measures with regards to vaccination are described in Section 6.1.

An independent medical reviewer will be appointed by the sponsor before the start of the study to perform review of the safety data during the study. Details regarding this role are provided in Section 10.7.

Symptoms of solicited local and systemic AEs will be collected in the diary in the evening after the vaccination and then daily for the next 7 days. Unsolicited AEs will be collected from vaccination until 28 days post-vaccination (Day 29). Serious adverse events and/or special reporting situations that are related to study

procedures will be reported from the time a signed and dated ICF is obtained onwards until the end of the study (Day 29). All other SAEs and/or special reporting situations will be reported from the day of vaccination onwards until 28 days post-vaccination.

Any clinically relevant changes must be recorded on the AE 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 11.1.3.

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 11.3.1.

Solicited Adverse Events

After vaccination, participants will remain under observation at the study site for at least 30 minutes for surveillance for any acute reactions, or longer if deemed necessary by the investigator. Symptoms of solicited local and systemic AEs will be collected in the diary in the evening after the 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/guardian and checked by a project field worker for 6 days. Day 8 of the diary will be completed by study site staff at the clinic. 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 AE.

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 6 days post-vaccination (day of vaccination and the subsequent 6 days). The extent (largest diameter) of any erythema and swelling should be measured (using the ruler supplied) and recorded daily. Day 8 of the diary will be completed by study staff at the site clinic.

- **Injection Site Tenderness**

  Injection site tenderness is a painful sensation localized at the injection site upon palpation or movement of the limb. Due to the 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).

- **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 the site of injection. 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.

Solicited Systemic Adverse Events

Parents/guardians 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 6 days at approximately the same time each day. The participant's temperature on Day 8 will be taken by study staff at the site clinic. If more than one measurement is made on any given day, the highest temperature of that day will be used in the CRF.

In this protocol, fever is defined as an endogenous elevation of body temperature ≥38° C, as recorded in at least one measurement.

Parents/guardians will also be instructed on how to note daily in the diary symptoms for 6 days post-vaccination (day of vaccination and the subsequent 6 days) any of the following events:

- body temperature
- fatigue/malaise
- chills
- headache
- nausea/vomiting
- muscle pain
- joint pain
- loss of appetite, in young children

Symptoms 7 days post vaccination (Day 8) will be assessed and recorded by study staff at the site clinic.

Physical Examination

A full physical examination will be performed at the screening visit. At subsequent study visits a brief, symptom-directed examination 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 (i.e. abnormalities) prior to vaccination (Day 1) are to be recorded as medical history, but after vaccination as an AE.

Vital Signs

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

Blood pressure and 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

A haematological assessment (i.e., full blood count) will be performed by the local laboratory at the time points indicated in the TIME AND EVENTS SCHEDULE. The investigator must review the laboratory report, document this review, and record any clinically relevant changes on the AE page and/or the screening page of the CRF. Laboratory reports must be filed with the source documents.

A full blood count will include:

-haemoglobin
-haematocrit
-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. An RBC evaluation may include abnormalities in the RBC count, or RBC morphology, which will then be reported by the laboratory.

8.3.2 Study Pausing Rules

The investigators and the sponsor's medical safety officer or delegate 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 safety officer or delegate will be involved in all discussions and decisions.

If any of the following events occur in any participant who received the study intervention, the site investigator will halt the vaccination of further participants in the study, and the sponsor's medical safety officer or delegate will be notified immediately:

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

   Note: All cases of death will be sent to the independent medical reviewer for information. Upon their review, the independent medical reviewer may then also advise whether a study pause is required.

2. One or more participants experience a SAE (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 causes other than vaccination with the study intervention.

To enable prompt response to a situation that could trigger pausing rules, the investigator should notify the sponsor's medical safety officer or delegate immediately and no later than 24 h after becoming aware of any related AE of grade 3 or above AND update the CRF with relevant information on the same day the AE information is collected. A thorough analysis of all grade 3 cases will be carried out by the sponsor's medical safety officer or designee, irrespective of whether the criteria for pausing the study are met. Based on the pausing criteria, the sponsor's medical safety officer or delegate then decides whether a study pause is warranted. All investigator(s) will be notified immediately in case of a study pause. The sponsor's medical safety officer or delegate is responsible for the immediate notification of independent medical reviewer and coordination of a meeting with the independent medical reviewer in case of a study pause.

The sponsor's medical safety officer or delegate or the investigator (upon consultation with the sponsor's medical safety officer or delegate) may contact the independent medical reviewer in any case in which, in their professional opinion, the safety of the participants or the reliability of the data could be affected.

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 independent medical reviewer, participant safety may be threatened.

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

8.4 IMMUNOGENICITY ASSESSMENTS

Venous blood samples for the determination of immune responses will be collected at the time points indicated in the TIME AND EVENTS SCHEDULE. Serum samples will be analysed to determine binding antibodies against EBOV GP using the FANG ELISA and neutralising antibodies against the Ad26 vector using the Ad26 VNA.

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 relevant laboratories.

8.4.1 Future scientific research

Future scientific research may be conducted to further investigate Ebola vaccine- and disease-related questions and to study other infections of public health importance in Sierra Leone and neighbouring countries. This may include the development of new, or the improvement of existing, techniques to characterise EBOV-directed immune responses or other diagnostic tests. No additional samples will be taken for these analyses, however, residual samples from the study tests may be retained for these purposes and analysed after the end of the study.

8.5 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.

9 PARTICIPANT COMPLETION/WITHDRAWAL FROM THE STUDY

9.1 COMPLETION

A participant will be considered to have completed the study if he or she has completed all assessments at the 28-day post-vaccination visit (Day 29).

Participants who prematurely discontinue the study intervention for any reason before completion of the 28-day post-vaccination visit will not be considered to have completed the study

9.2 WITHDRAWAL FROM THE STUDY

A parent/guardian has the right to withdraw their child from the study at any time for any reason. The investigator should make an attempt to contact the parent/guardian of a child who did not return for scheduled visits. Although a participant and/or parent/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 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/or the parent/guardian and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a participant withdraws, or a parent/guardian withdraws a participant, before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document.

A participant who wishes to withdraw consent, or a participant whose parent/guardian wishes to withdraw consent, will be offered an optional visit for safety follow-up (before the formal withdrawal of consent). The participant or participant's parent/guardian has the right to refuse this optional visit.

Withdrawal of Consent for the Use of Samples in Future Research

A participant, or a participant's parent/guardian, may withdraw consent for the use of samples for research (refer to Section 15.2.5). In such a case, every possible effort will be made to destroy samples after they are no longer needed for the study. Details of the sample retention for research are presented in the ICF.

10 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.

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

10.1 ANALYSIS SETS

Full Analysis Set: The full analysis set will include all participants with study intervention administration documented. This will be used for safety analysis.

Per-protocol Immunogenicity Population: The per-protocol immunogenicity population will include all vaccinated participants for whom immunogenicity data are available, excluding participants with major protocol deviations expecting to impact the immunogenicity outcomes.

10.2 SAMPLE SIZE DETERMINATION

Approximately 50 participants are expected to be enrolled into this trial (approximately 25 for each age group). The sample size is a convenience sample and is not based on formal hypothesis testing considerations.

10.3 PARTICIPANT INFORMATION

For all participants, demographic characteristics (e.g. age and sex), and other baseline characteristics (e.g. vital signs) will be tabulated and summarized with descriptive statistics.

10.4 SAFETY ANALYSES

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

Adverse Events (Including Reactogenicity)

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

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

Physical Examination

Because only abbreviated, symptom-directed examinations are performed per the discretion of the investigator, physical examination findings (i.e., abnormalities) after vaccination are to be recorded as AEs, and will be analysed and presented as indicated above. When reported prior to vaccination, they will be recorded as medical history.

Vital Signs

Descriptive statistics of temperature, blood pressure, 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 United States National Institutes of Health, National Institute of Allegy and Infectious Disease, Division of Microbiology and Infectious Diseases (DMID)

paediatric toxicity table (November 2007) (see Appendix 1) and in accordance with the normal ranges of the clinical laboratory. The most severe laboratory abnormalities following vaccination will be listed.

10.5 IMMUNOGENICITY ANALYSIS

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (e.g. geometric mean and 95% CI) 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 (i.e. responder rate), as applicable. Responders rate defined as >2.5-time increase over baseline value (or LLOQ) pre-dose 1 vaccination in the EBOVAC-Salone trial, will be calculated depending on availability of sample results from the EBOVAC-Salone trial.

10.6 INTERIM ANALYSIS

No interim analysis will be performed for this study.

10.7 INDEPENDENT DATA MONITORING COMMITTEE

An independent data monitoring committee (IDMC) will not be appointed for this study. The safety of the Ad26.ZEBOV vaccine has already been shown in children in previous studies. A booster dose of Ad26.ZEBOV was also shown to be safe in adults. There are no planned interim analyses. Thus the IDMC's role will be designated to an independent medical reviewer. The independent medical reviewer will be identified by the sponsor to review the accumulating safety data on an ongoing basis to ensure the continuing safety of the participants enrolled in this 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 8.2.) 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 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.

11 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 are conducted in accordance with those procedures.

Method of Detecting AEs and Serious Adverse Events

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

Solicited Adverse Events

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

Unsolicited Adverse Events

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

11.1 DEFINITIONS

11.1.1 Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable 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, including laboratory test abnormalities.

Note: For the time period of AE collection, see Section 11.3.

Serious Adverse Event

A SAE, 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 hospitalisation or prolongation of existing hospitalisation
- 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 (other than those listed above) , 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 AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis), the event must be reported as a suspected unexpected serious adverse reaction (SUSAR) (even after the study is over, if the sponsor, the independent medical reviewer, or the investigator becomes aware of it).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For Ad26.ZEBOV the expectedness of an AE will be determined by whether or not it is listed in the IB.

Adverse Event Associated With the Use of the Intervention

An AE is considered associated with the use of the intervention if the attribution is related by the definitions listed in Section 11.1.2.

An AE is considered not associated with the use of the intervention if the attribution is unrelated by the definitions listed in Section 11.1.2.

Adverse Events of Special Interest

AESIs (including potential AESIs) are significant AEs that are judged to be of special interest because of clinical importance, known or suspected effects of similar vaccines, or based on nonclinical signals. AESIs and potential AESIs will be carefully monitored during the study by the sponsor.

AESIs and potential AESIs must be reported to the sponsor within 24 hours of awareness, irrespective of seriousness (i.e., serious and nonserious AEs) or causality following the procedure described above for SAEs.

Specific requirements for the AESI are described below.

Thrombosis with Thrombocytopenia Syndrome (TTS)

TTS has been observed very rarely following vaccination with Janssen COVID vaccine and is considered to be an AESI in this study. TTS is a syndrome characterized by a combination of both a thrombotic event and thrombocytopenia. [13, 14]

Because this syndrome is rare and not completely understood, all cases of thrombosis and/or symptomatic thrombocytopenia will be considered a potential case of TTS and should be reported to the sponsor within 24 hours of awareness. Each potential AESI 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 2

and/or

- Symptomatic thrombocytopenia, defined as platelet count below LLN for the testing lab

Symptoms, signs, or conditions suggestive of a thrombotic event or symptomatic thrombocytopenia should be recorded and reported as a potential AESI 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 symptomatic thrombocytopenia, study site personnel should report the absolute value for the platelet count and the reference range for the laboratory test used.

For either a thrombotic event or symptomatic thrombocytopenia, it is recommended to test for anti-Platelet Factor 4 antibodies (anti-PF4) at the local laboratory or substitute local laboratory; repeat testing may be requested for confirmation upon sponsor discretion.

AESIs, including potential AESIs, will require enhanced data collection and evaluation. Every effort should be made to report as much information as possible about the event to the sponsor in a reasonable timeframe.

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 (e.g., American Society of Hematology 2021; British Society of Haematology 2021; CDC 2021). The use of heparin may be harmful and alternative treatments may be needed. Consultation with a hematologist is strongly recommended.

11.1.2 Attribution Definitions

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

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

Related

There is suspicion that there is a relationship between study intervention and AE (without determining the extent of that probability); there is a reasonable possibility that the study intervention contributed to the AE.

All AEs 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 AE; there are other more likely causes and administration of the study intervention is not suspected to have contributed to the AE.

All AE assessed as unrelated or doubtfully related to the study intervention will be considered unrelated to the study intervention.

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

11.1.3 Severity Criteria

All AEs, except for solicited AEs, will be coded for severity using a modified version of the November 2007 DMID paediatric toxicity table (see Appendix 1).

For AEs 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 (e.g. laboratory abnormalities).

11.2 SPECIAL REPORTING SITUATIONS

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

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

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

11.3 PROCEDURES

Depending on the nature of the event, the reporting procedures below will be followed. Any questions concerning AE reporting will be directed to the sponsor. Further details on AE reporting can be found in the AE reporting flowchart.

11.3.1 All Adverse Events

Symptoms of solicited local and systemic AEs will be collected in the diary in the evening after the vaccination and then daily for the next 7 days. Unsolicited AEs will be reported from vaccination until 28 days post-vaccination.

Serious adverse events and/or special reporting situations that are related to study procedures will be reported from the time a signed and dated ICF is obtained onwards until the end of the study. All other SAEs and/or special reporting situations will be reported from the day of vaccination onwards until 28 days post-vaccination. 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 analyse the study data including all AE 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 AEs will be deemed related to study intervention or not related to study intervention, according to Section 11.1.

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

All AEs, 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 aetiology (e.g., 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 AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The LSHTM assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The LSHTM will also report to the vaccine manufacturer and investigator (and the head of the investigational institute, as required) all SUSARs. The investigator (or sponsor, as required) must report SUSARs to the appropriate IEC that approved the protocol unless otherwise required and documented by the IEC.

Janssen Vaccines & Prevention B.V., as the vaccine manufacturer, will report any SUSAR to all the investigators of studies using the experimental vaccine.

The parent/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 child 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)
- Participant number

11.3.2 Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate person nominated by the sponsor by study-site personnel within 24 hours of their knowledge of the event and to IEC and local regulatory authority, as required.

Information regarding SAEs will be transmitted to the sponsor and to IEC and local regulatory authority, as required, using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor, IEC and local regulatory authority, within 24 hours. The initial and follow-up reports of a SAE should scanned and sent by email.

All SAEs 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 SAE. Any event requiring hospitalisation (or prolongation of hospitalisation) that occurs during the course of a subject's participation in a study must be reported as a SAE, except hospitalisations for the following:

- Hospitalisations not intended to treat an acute illness or AE (e.g., social reasons such as pending placement in a long-term care facility)
- Surgery or procedure planned before entry into the study (this must be documented in the CRF).

  Note: Hospitalisations that were planned before the signing of the ICF, and where the underlying condition, for which the hospitalisation was planned, has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalisation is to be reported as a new SAE.

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 SAE.

11.4 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.

12 PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., 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. Janssen Vaccines & Prevention B.V. and the sponsor have 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.

12.1 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 SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 11.3). A sample of the suspected product should be maintained for further investigation if requested by the sponsor and Janssen Vaccines & Prevention B.V.

12.2 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.

13 STUDY INTERVENTION INFORMATION

Ad26.ZEBOV

Ad26.ZEBOV is a monovalent, replication-incompetent adenovirus serotype 26-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 IB for a list of excipients.

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

13.1 PACKAGING

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

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

13.2 LABELLING

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

13.3 PREPARATION, HANDLING, 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 equipment for storage of the study intervention (including refrigerators, freezers) must be equipped with a continuous temperature monitor and alarm, and with back-up power systems. In the event that the 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.

Full details on the preparation, the holding time, and storage conditions from the time of preparation to delivery of Ad26.ZEBOV are provided in the Site Investigational Product Procedures Manual.

13.4 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 or delegate 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. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study site agreed upon with the sponsor.

14 STUDY -SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- IB and Addendum (if applicable) for Ad26.ZEBOV
- Site Investigational Product Procedures Manual
- Laboratory manual
- Electronic Data Capture (eDC) Manual/electronic CRF Completion Guidelines
- Sample ICF
- Participant diaries
- TOU
- Rulers, thermometers
- Participant wallet card

15 ETHICAL ASPECTS

15.1 STUDY-SPECIFIC DESIGN CONSIDERATIONS

Potential participants, and/or their parent/guardian, will be fully informed of the risks and requirements of the study. During the study, participants and/or their parent/guardian will be given any new information that may affect their decision to continue participation. They will be told that their consent 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 parents/guardians of participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be allowed to enrol their child.

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

When referring to the signing of the ICF, the term guardian refers to the traditionally or legally appointed guardian of the child with authority to authorise participation in research. For each participant, his or her parent or guardian, must give permission and written consent (according to local requirements) after the nature of the study has been fully explained and before any study-related activities are performed. Only parents/guardians who are fully able to understand the risks and benefits, and who provide their consent voluntarily, can enrol their child into the study. Assent must be obtained from children capable of understanding the nature of the study, typically potential participants 7 years of age and older. For the purposes of this study, all references to participants who have provided consent (and assent as applicable) refer to the participant and his or her parent/guardian who has provided consent according to this process. Children who assent to a study and later withdraw that assent will not be maintained in the study against their will, even if their parent/guardian still want them to participate.

Test of Understanding

The TOU is a short assessment of the parent/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/guardian understands the study and their requirements for participation of their child.

The parent/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/guardian. The parent/guardian must subsequently sign the ICF, indicating that he or she is willing to allow their child to participate in the study.

If a parent/guardian fails to achieve the passing score on an attempt, further information and counselling will be provided to the parent/guardian by a study team member. The parent/guardian is allowed to retake the test twice to achieve the passing score (≥90%) required for participation of their child in the study. If the parent/guardian fails to achieve the passing score on the third attempt they will not be able to re-take the test again, and their child will not be allowed to participate in the study.

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 enrol their child.

15.2 REGULATORY ETHICS COMPLIANCE

All references to the IEC refer to the LSHTM Ethics Committee and the Sierra Leone Ethics and Scientific Review Committee.

15.2.1 Investigator Responsibilities

The investigator will be 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.

GCP 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.

15.2.2 Independent Ethics Committee

Before the start of the study, the investigator (or sponsor where required) will provide the IEC 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 study subjects, e.g. diary)
- IB (or equivalent information) and amendments
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to study participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for study participants
- Any other documents that the IEC requests to fulfil its obligation

This study will be undertaken only after the IEC has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study

conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programmes, and after the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC and the documents being approved.

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data, or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- New or revised participant recruiting materials approved by the sponsor (when applicable)
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study vaccine
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the centre
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC

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

At least once a year, the IEC 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 about the study completion.

15.2.3 Informed Consent

In this community-based study, informed consent will take place at several levels ranging from approval from the government authorities, followed by community level consent, and finally, individual consent.

Approval from Respective Health Authorities

Approval for this project will be obtained from the respective health authorities in the country where the study is conducted.

Additionally, during the planning process of the study, approval will be sought from other authorities such as district or local councillors, political leaders, and traditional leaders.

Consent at the Community Level

Documented community-level consent by a community leader must be available.

Consent at the Individual Level

The parent/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 has been fully explained. The ICF 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 and be in a language that the legally acceptable representative and 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 enrolment in the study, the investigator or an authorized member of the study-site personnel must explain to the subject and/or the subject's legally acceptable representative the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. The subject and/or the legally acceptable representative will be informed that their participation/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 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 their child's health status. It also denotes that the legally acceptable representative agrees to allow his or her child's study physician to recontact the them 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 their child's 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 legally acceptable representative.

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 the impartial witness should personally date and sign the ICF after the consent of the legally acceptable representative is obtained.

Children will be enrolled only after obtaining consent of a parent/guardian. Assent will be obtained from children capable of understanding the nature of the study, typically subjects 7 years of age and older. Written assent will be obtained from subjects who are able to write. Children who assent to a study and later withdraw that assent will not continue in the study against their will, even if their parent/guardian still want them to participate.

Children who turn 7 years of age will be asked to provide assent, if it is deemed they are able to comprehend the information provided, for continuation in the study at the first available opportunity.

15.2.4 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 participants 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 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.

15.2.5 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. Future scientific research may be conducted to further investigate Ebola vaccine- and disease-related questions and to study other infections of public health importance in Sierra Leone and neighbouring countries. This may include the development of new or the improvement of existing techniques to characterize EBOV-directed immune responses or diagnostic tests. No additional samples will be taken for these analyses, however, residual samples from other tests may be retained for these purposes and analysed after the end of the study.

Parents/guardians 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 study without having their blood samples stored for future testing (see also Section 9.2). 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.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Parents/guardians may withdraw consent for their child's samples to be stored for research at any time during the study.

16 ADMINISTRATIVE REQUIREMENTS

16.1 PROTOCOL AMENDMENTS

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments will be issued by the sponsor, and signed and dated by the relevant investigator. Protocol amendments will not be implemented without prior IEC approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment will be promptly submitted to the IEC and relevant competent authority. Documentation of amendment approval by the investigator and IEC will be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC (where required) will 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 will be made before implementing any departure from the protocol. In all cases, contact with the sponsor will 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.

16.2 REGULATORY DOCUMENTATION

16.2.1 Regulatory Approval and Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authority in the country where the study is being conducted. A study may not be initiated until all local regulatory requirements are met. All references to the local Regulatory Authority refer to the Pharmacy Board of Sierra Leone.

16.2.2 Required Pre-study Documentation

The following documents will 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 approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant 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 authorised designee.
- Name and address of the IEC, including a current list of the IEC members and their function, with a statement about how it is organised and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC, 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, 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
- Signed and dated statement of investigator (e.g. Form FDA 1572), If applicable
- Documentation of investigator qualifications (e.g. curriculum vitae)
- Completed investigator financial disclosure form from the Principal Investigator, where required
- Signed and dated clinical trial agreement, which includes financial agreement
- Any other documentation required by local regulations

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

- Completed investigator financial disclosure forms from all sub investigators
- Documentation of sub-investigator qualifications (e.g., 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

16.3 SUBJECT IDENTIFICATION AND ENROLMENT LOGS

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

The participant identification and enrolment 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.

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

16.4 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 AEs and follow-up of AEs; 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 TOU and participant's diary used to collect information regarding solicited symptoms after vaccination will be considered source data.

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (e.g., physical examination, laboratory assessment) and documented in the source documents.

16.5 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 case report form (eCRF). Study-specific data will be transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documentation. Data must be entered into eCRFs in English. Study site personnel must complete the eCRF promptly after a participant 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 eCRF, 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.

16.6 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 and/or remote monitoring 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 CRFs for accuracy and completeness during onsite monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. The data will be entered into the study database and verified for accuracy and consistency with the data sources.

Representatives of the sponsor may visit the participating site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and/or LSHTM policy. Similar procedures may also be conducted by a regulatory authority. Further details of on-site audit policies are presented in Section 16.10.

16.7 RECORDS RETENTION

In compliance with ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each participant, 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.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, as per LSHTM SOP (LSHTM-SOP-049 Site Close out).

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.

16.8 MONITORING

The sponsor, or their delegate, will perform study site visits to monitor this study.

The sponsor, or their delegate 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 enrolment 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) (e.g., 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 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.

16.9 STUDY COMPLETION/TERMINATION

16.12.1 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.

16.12.2 Study Termination

The sponsor reserves the right to close the study for data collection or terminate the study at any time for any reason at the sole discretion of the sponsor. The study will be closed upon study completion. The study is considered closed when all the 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 the study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirement of the IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator

- Discontinuation of further study intervention development

16.10 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.

16.11 USE OF INFORMATION AND PUBLICATION

All information, including but not limited to information regarding the Ad26.ZEBOV vaccine or the sponsor's operations (e.g., 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. 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 or the vaccine manufacturer, Janssen Vaccines & Prevention B.V., in connection with the continued development of the Ad26.ZEBOV and MVA-BN-Filo vaccine regimen, 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.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary data and information without approval from the investigator. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the International Committee of Medical Journal Editors (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.

APPENDIX 1

Toxicity Grading Scale for Healthy Paediatric Participants (older than 3 months) Enrolled in Preventive Vaccine Clinical Trials

Adapted from: DMID° Pediatric Toxicity Tables (November 2007, draft). For adverse events not included in the tables below, refer to the severity criteria guidelines in section 11.1.3 Severity Criteria. 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/mm³**	**400-749/mm³**	**250-399/mm³**	**<250/mm³**
Platelets	75,000-99,999/mm³	50,000-74,999/mm³	25,000-49,999/mm³	<25,000/mm³
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 2:

THROMBOTIC EVENTS TO BE REPORTED AS POTENTIAL ADVERSE EVENTS OF SPECIAL INTEREST

The list of thrombotic events to be reported to the sponsor as potential AESIs 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

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