Safety and immunogenicity of an Ad26.ZEBOV booster vaccine in Human Immunodeficiency Virus Positive (HIV+) adults previously vaccinated with the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen against Ebola: a single-arm, open-label Phase II clinical trial in Kenya and Uganda.

SUPPLEMENTARY MATERIAL

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1. Supplementary Tables

Table S1: Participant haematology and HIV assessments at screening for enrolment. Full blood count, CD4+ T cell count, and HIV viral load measurement were performed by local laboratories at the screening visit, within 28 days prior to booster vaccination.

Full analysis set	Total (N=26)
Haemoglobin, g/dl	
Mean (SD)	14.1 (1.4)
Median (Q1; Q3)	14.1 (11.3; 16.8)
WBC, × 10^9/L	
Mean (SD)	5.5 (1.4)
Median (Q1; Q3)	5.1 (2.8; 9.8)
Low WBC[1], n (%)	1(4)
LYM, × 10^9/L	
Mean (SD)	2.6 (0.6)
Median (Q1; Q3)	2.4 (1.6; 4.6)
MON, × 10^9/L	
Mean (SD)	0.4 (0.1)
Median (Q1; Q3)	0.3 (0.1; 0.7)
Low MON[1], n (%)	1(4)
GRA, × 10^9/L	
Mean (SD)	4.8 (0.5)
Median (Q1; Q3)	4.7 (4.0; 5.6)
Platelets, × 10^9/L	
Mean (SD)	265.4 (61.1)
Median (Q1; Q3)	259.0 (190.0; 494.0)
CD4 count, cells/µL[2]	
Mean (SD)	808.8 (175.3)
Median (Q1; Q3)	828 (519; 1130)
HIV viral load, copies/mL	
Not detected, n (%)	13 (50)
< 40, n (%)	12 (46)
45, n (%)	1 (4)

Granulocytes (GRA); lymphocytes (LYM); monocytes (MON); first quartile (Q1); third quartile (Q3); standard deviation (SD); white blood cells (WBC).

[1]Classified according to age and sex specific normal ranges of the local laboratory.
[2]Calculated based on 25 reported CD4 counts (one participant with CD4 count reported as >2000 was not included in calculation).

Table S2. Unsolicited adverse events summary

Full analysis set	**Total (N = 26)** n (%)
Unsolicited adverse events (AEs),	**12 (46)**
Infections and infestations	**5 (19)**
Upper respiratory tract infection	3 (12)
Urinary tract infection	2 (8)
Otitis media	1 (4)
Vaginal candidiasis	1 (4)
Gastrointestinal disorders	**2 (8)**
Acute gastritis	1 (4)
Gastroesophageal reflux disease	1 (4)
Nervous system disorders	**2 (8)**
Headache	2 (8)
Musculoskeletal and connective tissue disorders	**2 (8)**
Low back pain	2 (8)
Neck pain	1 (4)
Metabolism and nutrition disorders	**2 (8)**
Diabetes	1 (4)
Anorexia	1 (4)
Blood and lymphatic system disorders	**1 (4)**
Lymphadenopathy axillary	1 (4)
Cardiac disorders	**1 (4)**
Chest heaviness	1 (4)
Vascular disorders	**1 (4)**
Diastolic hypertension	1 (4)

AEs are coded using MedDRA version 23.1
n (%): number (percentage) of participants with 1 or more event

2. EBL2010 Study Group

EBL2010 STUDY GROUP (October – November 2021)

LSHTM, UK

Chief investigator: Prof. Deborah Watson-Jones

Investigator: Prof. Brian Greenwood

Trial Coordinators: Edward Choi, Daniela Manno, Victoria Ewing

Assistant Trial Coordinator: Julie Foster

Senior Project Managers: Stuart Malcolm, Jennifer Brown

Project Managers: Isbel James, Agatha Ojugo, Camille Le Baron

Project Assistants: Claudine Massin-Shepherd

Data Manager: Yusupha Njie

Statistician: Philip Ayieko

Laboratory Director: Brett Lowe

Laboratory Manager: Bolarinde Lawal

Laboratory Scientist: Otieno Tuda Godfrey

Quality Manager: Nicholas Connor

Study Responsible Physician: Kambale Kasonia

Medical Safety Officers: Mateus Kambale Sahani, Badara Cisse

MRC/UVRI & LSHTM Uganda Research Unit, Uganda

Study Investigators
Principal Investigator: Prof. Kaleebu Pontiano

Investigator: Dr Anywaine Zacchaeus

Investigator: Dr Ggayi Abu-Baker Mustapher

Investigator: Dr Jonathan Kitonsa

Investigator: Dr Freddie Mukasa Kibengo

Site coordination and medical team
Trial Manager: Anywaine Zacchaeus

Trial Coordinator: Ggayi Abu-Baker Mustapher

Administration & project management
Sarah Kizito – Field Station Administrator

Kenneth Wassajja Kayemba – Field IT Administrator

Amodoi Gertrude – Field IT assistant

Kiyemba Baker – Administrative Assistant (housekeeping)

Nanteza Mariam – Head of Research Support Office (contracts and grant management)

Monica Badaru – Head of Finance

Biometric & registration
Ssebunya Baker – Field Technical Assistant

Kiwanuka Ronald – Field Technical Assistant

Communications
Pamela Wairagala Nabukenya – Head of Communications

Basajja Vincent – Community Liaison Officer

Community engagement
Basajja Vincent – Community Liaison Officer

Masawi Sylvia – Community Liaison Officer

Ssebunya Baker – Field Technical Assistant

Kiwanuka Ronald – Field Technical Assistant

Data management
Kakande Ayoub – Head of Data Management and Archives

Kafeero Paddy Lwakataka – Data Manager

Nabukenya Shamim – Data Manager

Nasejje Shanila – Data Entry and Archivist

Bbosa Fulgensio – Data Entry Intern

Field work
Ssebunya Baker – Field Technical Assistant

Kiwanuka Ronald – Field Technical Assistant

Laboratory
Nambaziira Florence – Head of Clinical Diagnostic Laboratory (CDLS) for safety labs

Tobias Vudriko – Site Laboratory Manager (safety labs, sample storage and shipping)

Nabanoba Esther – Laboratory Technologist

Nanyunja Regina – Laboratory Technologist (CD4 count and viral load)

Muhigirwa Edward – Laboratory Technologist

Mushabe Didas (RIP) – Laboratory Technologist

Kisakye Flavia – Laboratory Technologist (sample shipment)

Oliver Nantume – Laboratory Technologist,

Nassali Joanita – Laboratory Data Manager

Nurses
Naluynda Hadijah – Nursing Officer (Nurse lead and QC)

Nandhego Julian – Study Nurse

Nalubega Cissy Lillian - Nursing Officer (QC)

Pharmacy & Cold Chain
Phiona Kaweesi Nabaggala – Study Pharmacist

Kakeeto Wilson – Pharmacy Technician (cold chain, IP preparation and accountability)

Kyeyune Mugagga - Pharmacy Technician (cold chain, IP preparation)

Taire Paul - Pharmacy Technician (cold chain, IP preparation)

Quality Assurance

Dr Geofrey Kimbugwe – Head of Research Compliance and Quality Assurance

Musemeza Stephen – Quality Assurance Officer

Bengo Samuel – Regulatory Officer

KAVI – Institute of Clinical Research, Kenya

Principal Investigator: Prof. Omu Anzala

NAME	FIRST NAME	LAST NAME	DEPARTMENT	TITLE
Geoffrey Ombati	Geoffrey	Ombati	Clinic	Clinical Officer
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Judith Omungo	Judith	Omungo	Clinic	Nurse Counsellor
Hilda Ogutu	Hilda	Ogutu	Clinic	Nurse Counsellor
Jacquelyn Nyange	Jacquelyn	Nyange	Clinic	Regulatory Officer
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Sharon N. Lipesa	Sharon	Lipesa	Clinic	Community Liason Officer
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Timothy Kotikot	Timothy	Kotikot	Clinic	Clinical Officer
Catherine Sereti	Catherine	Sereti	Clinic	Nurse Counsellor
Dr. Michael Mutua	Michael	Mutua	Clinic	Trial Physician / Medical Manager
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Irene Mugenya	Irene	Mugenya	Clinic	Trial Physician
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Simon Waweru	Simon	Waweru	IT-Data	IT-Data Officer
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Irene Mwangi	Irene	Mwangi	Laboratory	Lab Manager
Brian Onsembe	Brian	Onsembe	Laboratory	Laboratory Technologist
John Gachie	John	Gachie	Laboratory	Laboratory Technologist / Deputy Quality Assurance Manager
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Roseline Shichenga	Roseline	Shichenga	Pharmacy	Pharmaceutical Technologist

Independent Medical Reviewer
Peter Bock, Desmond Tutu TB Centre, Stellenbosch University, South Africa

Janssen Vaccines and Prevention, Leiden, The Netherlands
Michael Katwere, Study Responsible Physician

Babajide Keshinro, Study Responsible Physician

Chelsea McLean, Biomarker Lead

Cynthia Robinson, Medical Leader

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Auguste Gaddah, Statistician

Karolien Preckler, Global Trial Leader

VAC52150EBL2010

An open label, Phase 2 study to evaluate the safety and immunogenicity of an Ad26.ZEBOV booster dose in Human Immunodeficiency Virus Positive (HIV+) adults previously vaccinated with the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen

Protocol VAC52150EBL2010; Phase 2

Innovative Medicines Initiative

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

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

Version 1.0, 13 November 2020

	NUMBER	DATE
FINAL VERSION	1.0	13 Nov 2020
AMENDMENT (if any)		

Sponsor
London School of Hygiene & Tropical Medicine is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact:

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Funder
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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
AIDS	acquired immunodeficiency syndrome
AE	adverse event
ARV	antiretroviral agent
β-hCG	beta human chorionic gonadotropin
CI	confidence interval
CRF	case report form
DAIDS	Division of AIDS
EBOV	Ebola virus
eCRF	electronic case report form
eDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EVD	Ebola virus disease
FANG	Filovirus Animal Non-Clinical Group
GCP	Good Clinical Practice
GP	glycoprotein
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
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
IRB	Institutional Review Board
KAVI	Kenya AIDS Vaccine Initiative
LSHTM	London School of Hygiene & Tropical Medicine
MedDRA	Medical Dictionary for Regulatory Activities
µL	microlitres
mL	millilitres
MVA-BN-Filo	Modified Vaccinia Ankara Bavarian Nordic vector expressing multiple filovirus proteins
PCR	polymerase chain reaction
PQC	Product Quality Complaint
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
TOU	Test of Understanding
UVRI	Uganda Virus Research Institute
VISP	vaccine induced seropositivity
vp	viral particle(s)
WHO	World Health Organization

SYNOPSIS

TITLE

An open label, Phase 2 study to evaluate the safety and immunogenicity of an Ad26.ZEBOV booster dose in Human Immunodeficiency Virus positive (HIV+) adults previously vaccinated with the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen.

RATIONALE

In previous Phase 2 and 3 trials, vaccination of HIV positive adult participants with the 2-dose Ebola vaccine regimen (Ad26.ZEBOV, followed by MVA-BN-Filo) elicited humoral immune responses comparable to those in HIV negative adults 21-days after dose 2. However, the durability of vaccine-induced humoral responses was not known.

PRIMARY OBJECTIVES

- To assess the safety and tolerability of a Ad26.ZEBOV booster dose in HIV positive adults previously vaccinated with the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen.

- To assess humoral responses induced by the booster dose against EBOV glycoprotein (GP), as measured by Filovirus Animal Non-Clinical Group (FANG) Enzyme-Linked Immunosorbent Assay (ELISA) at 7 and 21 days.

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 to evaluate the immune response to a booster dose of adenovirus serotype 26 expressing the Ebola virus Mayinga glycoprotein (Ad26.ZEBOV) administered to HIV positive participants who previously received the 2-dose Ebola vaccine regimen with Ad26.ZEBOV followed by Modified Vaccinia Ankara Bavarian Nordic vector expressing multiple filovirus proteins (MVA-BN-Filo) 28 days or 56 days later in East Africa. Only participants who received the Ad26.ZEBOV and MVA-BN-Filo regimen during their participation in the VAC52150EBL2002 vaccine trial are eligible for enrolment in this study. The Ad26.ZEBOV will be administered as a booster dose in this population approximately 4 years from the time they received dose 2 (MVA-BN-Filo).

Approximately 50 HIV positive adult participants, aged 18 - 50 years at randomisation in the parent trial, VAC52150EBL2002, from Kenya and Uganda who previously received the 2-dose Ebola vaccine regimen will be invited to participate in this trial. Subjects will be asked to consent to participate in this study. Upon receiving the booster vaccination, participants will be followed up for immunogenicity and safety for approximately 28 days (+/- 3 days).

SUBJECT POPULATION

Participants must be healthy (based on physical examination, medical history, and clinical judgment) HIV-positive adults who received the Ad26.ZEBOV and MVA-BN-Filo vaccine regimen in the VAC52150EBL2002 trial and were aged ≥18 to ≤50 years at the time of randomisation to that study. They will have to be virologically suppressed and immunologically controlled on their highly active antiretroviral therapy (HAART) regimen (HIV viral load < 50 copies/millilitres (mL) and CD4+ T cell count >/= 350 cells/microlitres (μL) within 28 days of study vaccination). The study will be conducted at VAC52150EBL2002 sites in Kenya and Uganda.

INVESTIGATIONAL PRODUCT, DOSAGE AND ADMINISTRATION

Ad26.ZEBOV is a replication-incompetent monovalent vaccine against Ebola. It consists of an adenovirus serotype 26 vector expressing the full-length Ebola virus (EBOV, formerly known as Zaire ebolavirus) Mayinga GP, and is produced in the human cell line PER.C6®.

A single dose of Ad26.ZEBOV at a dose of $5x10^{10}$ viral particles (vp) will be administered intramuscularly.

SAFETY EVALUATIONS

Solicited local (i.e. injection site) and systemic adverse events will be assessed on the day of vaccination and using a diary for a period of seven days following the booster vaccination. Unsolicited adverse events will be tracked for 28 days following booster vaccination, while serious adverse events will be tracked for the duration of the study. The Principal Investigators, together with the sponsor's medical safety officer, will be responsible for the safety monitoring 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 Kenya and Uganda, and neighboring countries. This may include the development of new, or the improvement of existing, techniques to characterise 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 conducted when all participants have completed the 28-days post- booster visit or discontinued earlier. This analysis will include all available data up to this point.

Sample Size Determination

Approximately 50 HIV seropositive adult participants will be enrolled into this trial. This number is based on the potentially available HIV seropositive participants in VAC52150EBL2002 who previously received the 2-dose Ebola vaccine regimen (Ad26.ZEBOV followed by MVA-BN-Filo) following a day 0,56 or 0,28 schedule at sites in Kenya and Uganda.

SAFETY ANALYSES

No formal statistical testing of safety data is planned. Safety data will be analysed descriptively.

IMMUNOGENICITY ANALYSES

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (observed values and changes from booster vaccination, including geometric mean and 95% confidence intervals [CIs], as appropriate) will be calculated for continuous immunologic parameters at each time point analysed. Graphical representations of changes in immunologic parameters will be prepared, as applicable. Frequency tabulations will be calculated for discrete (qualitative) immunologic parameters at each time point analysed.

Frequency tabulations will be calculated for discrete (qualitative) immunologic parameters (i.e. responder rate), as applicable.

TIME AND EVENTS SCHEDULE

Study Procedures	Screening (≤28 days[j])	Study Period				
		Day 1 Booster	Days 1-7	Day 8 (+3 days)	Day 22 (±3 days)	Day 29[a] (± 3 days)
Test of Understanding (TOU)[bc]	X					
Informed consent[d]	X					
Medical history and demographics	X					
Inclusion/exclusion criteria[e]	X					
Urine pregnancy test[f]	X	X				
Physical examination[g]	X	X[h]		X	X	X[a]
Vital signs[i]	X	X		X	X	X[a]
Vaccine Administration [d]		X				
30 minute post-vaccination observation[j]		X				
Distribution of participant diary		X				
Completion of diary at home[k]			X			
Completion and review of diary by study site personnel				X		
Solicited adverse events recording		X	X[k]	X		
Unsolicited adverse events recording[l]		From vaccination (Day 1) onwards until 28 days post-vaccination[m]				
Serious Adverse Events [n]	Continuous					
Concomitant medications [o]	X	X	X	X	X	X
Blood draw						
Haematology (full blood count) [p]	X					
HIV viral load assay and CD4+ T-cell count assessment [q]	X					
Immunogenicity (serum)		X[h]		X	X	
Approximate blood draw volumes						
Haematology: 2 mL per blood draw [p]	2.0					
HIV assessments :10 mL per blood draw [q]	10.0					
Immunogenicity: 10 mL per blood draw		10.0		10.0	10.0	
Cumulative total (maximum) (mL)	**12.0**	**10.0**		**10.0**	**10.0**	

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

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[a] 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, data on physical examination and vital signs cannot be collected or recorded for this visit.

[b] If required for use by the site.

[c] The TOU should be administered to the participant after reading, but before signing, the informed consent form, please see Section 15.1.

[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 screening period and before the vaccination on Day 1. If a participant's clinical status changes (including the receipt of clinically significant laboratory results or additional medical records) after screening but before Day 1 such that the participant no longer meets all eligibility criteria, then the participant will be excluded from participation in the study.

[f] Only for women of childbearing potential.

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

[h] Prior to study vaccine administration.

[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 and systemic and unsolicited adverse events emerging during the observation period will be recorded in the CRF.

[k] Participants will use the participant diary to document solicited local and systemic adverse events (reactogenicity) in the evening after the booster vaccination and then daily for the next 6 days at approximately the same time each day. Diaries should be completed at home by the participant from Day 1 – Day 7, Day 8 of the diary will be completed at the study clinic by a study doctor or nurse.

[l] Non-serious adverse events will be reported until 28 days after the vaccination. Pregnancies will be reported from signing of the informed consent form until the end of the study.

[m] Participants will be instructed to contact the investigator before the next visit if they experience any adverse event or intercurrent illness they perceive as relevant and/or possibly related to the study vaccine in their opinion.

[n] 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 the first vaccination onwards until the end of the study.

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

[p] A safety haematology blood test will be performed at screening to obtain baseline values on full blood count

[q]At screening, a blood sample for HIV viral load and CD4+ T-cell count will be collected.

1 INTRODUCTION

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

Janssen Vaccines & Prevention B.V., in collaboration with Bavarian Nordic GmbH Denmark and in conjunction with an Innovative Medicines Initiative EBOVAC1 consortium led by the London School of Hygiene and Tropical Medicine (LSHTM), including the Institut National de la Santé et de la Recherche Médicale, University of Sierra Leone College of Medicine and Health Sciences, and University of Oxford as partners, is investigating the potential of a prophylactic Ebola vaccine regimen (VAC52150) comprised of the following two candidate Ebola vaccines:

Ad26.ZEBOV is a non-replicating, monovalent vaccine expressing the full-length Mayinga 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 responsible for the 2013-2016 epidemic in West Africa had 97% homology to the EBOV GP used in these vaccine regimens.

For the most up-to-date nonclinical and clinical information regarding Ad26.ZEBOV please refer to the latest versions of the Investigator's Brochure (IB) 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

Clinical studies

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 HIV-seropositive adults, 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 adult participants

Unblinded safety data from 2,390 adults from studies (EBL1001, EBL1002, EBL1003, EBL1004, EBL2001, EBL2002, EBL3001, EBL3002, EBL3003, and FLV1001), including 1,814 healthy and 118 HIV+ adults dosed with Ad26.ZEBOV, MVA-BN-Filo [N=1,932], and 434 healthy and 24 HIV+ adults dosed with control (placebo or active control, [N=458]) is summarised here. Overall, the safety profile consists of mild to moderate adverse events (AEs) of short duration with no sequelae, confirming results of the Phase 1 studies. No safety signals were identified. The frequency of Grade 3 pyrexia (≥39.0°C) was <1% following vaccination and the incidence of any febrile response was <7.5% in any group (Table 1). Serious adverse events (SAEs) were reported in 54 participants (2.8%)

vaccinated with the active vaccine regimen and in 11 participants (2.4%) vaccinated with control. (Table 1).

No specific safety concern was raised in the HIV+ population.

Table 1 Frequency of Solicited and Unsolicited Adverse Events in Adults – by Dose

	Adverse Events					
	Ad26.ZEBOV N=1,932		MVA-BN-Filo N=1,672		Control [a] N=850	
	n	%	n	%	n	%
Overall solicited AEs	1,449	75.0	1,075	64.3	467	54.9
Overall solicited local AEs	1,004	52.0	830	49.6	181	21.3
Overall solicited systemic AEs	1,294	67.0	750	44.9	381	44.8
Most frequent local solicited AE (injection site pain)	928	48.0	770	46.1	150	17.6
Most frequent systemic solicited AE (fatigue)	900	46.6	505	30.2	219	25.8
Any fever (defined as ≥38°C)	143	7.4	64	3.8	29	3.4
Any solicited Grade 3	85	4.4	27	1.6	15	1.8
Any solicited local Grade 3	18	0.8	11	0.7	0	0
Any solicited systemic Grade 3	81	4.2	24	1.4	15	1.8
Grade 3 fever (defined as ≥39°C)	17	0.9	10	0.6	6	0.7
Overall unsolicited AEs	729	37.7	564	33.7	323	38.0

N: Number of doses of Ad26.ZEBOV, MVA-BN-Filo or placebo from studies EBL1001, EBL1002, EBL1003, EBL1004, EBL2001, EBL2002, EBL3001, EBL3002, EBL3003, and FLV1001 from regimens where Ad26.ZEBOV at the clinical dose was administered as the first dose followed by MVA-BN-Filo as the second dose when at least 28 days had elapsed between the first and second doses. Includes HIV+ and healthy adults.

[a] Placebo or active control (MenACWY in study EBL3001).

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

An Ad26.ZEBOV booster vaccination was given to 29 adult participants, who were vaccinated approximately two years before with Ad26.ZEBOV followed by MVA-BN-Filo 56 days later in the VAC52150EBL3001 (EBOVAC Salone) study 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 (4). In the VAC52150EBL2002 study, 73 HIV negative participants in Cohort 1 who received the 2-dose Ad26.ZEBOV/MVA-BN-Filo regimen, either 28 or 56 days apart, were also given an Ad26.ZEBOV booster dose one year after dose 1. The booster dose elicited a strong anamnestic response in 100% of these participants (5).

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. 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 EBOV. 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 (6).

If the Ad26.ZEBOV booster dose is shown to be safe and immunogenic in HIV-positive adults as in HIV-negative adults, the participants enrolled in this study may benefit from the potential prolonged protection 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 is being evaluated in a number of completed and ongoing clinical studies in adults and children. The vaccine is well tolerated, with no safety concerns identified. The vaccine mainly elicited some solicited local and systemic reactions, as expected with injectable vaccines, and 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 version 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. These events will be monitored, but are generally short-term and do not require treatment.

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

Risks from Blood Draws

As with all clinical studies requiring blood sampling, there are risks associated with venipuncture and multiple blood sample collection. Blood drawing may cause pain, tenderness, bruising, bleeding, dizziness, vaso-vagal response, syncope, and, rarely, infection at the site where the blood is taken. The total blood volume to be collected is considered to be an acceptable amount of blood over this time period from the population in this study (see Section 15.1)

Concomitant Vaccination

Concomitant vaccination might have an influence on both safety profile and immunogenicity of a booster of Ad26.ZEBOV. Likewise, the study intervention might have an influence on both safety profile and immunogenicity of any concomitant vaccination. Therefore, a participant should not receive a live-attenuated vaccine from 30 days before the vaccination until 30 days after the vaccination unless a vaccine preventable disease such as measles emerges which would warrant administration of live-attenuated vaccines. Immunisations with inactivated vaccines should be administered at least 15 days before or after administration of any study intervention in order to avoid any potential interference in efficacy of the routine immunisations 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.

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 the vaccine.

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

Unknown Risks

There may be other risks that are not known. If any significant new risks are identified, the Principal Investigators and participants will be informed.

1.2.4 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 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 minimise the risk and protect the well-being of participants in the study.

- Several safety measures are included in this protocol to minimise the potential risk to participants, including the following:

    - Participants will remain at the site for at least 30 minutes after the 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 SAEs 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 occur at the scheduled time for vaccination, the participant may be rescheduled for vaccination at a later time point within the window allowed for screening (≤28 days prior to Day 1 vaccination), 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

In previous Phase 2 and 3 trials, HIV negative adult participants who were immunised with the 2-dose Ebola vaccine regimen (Ad26.ZEBOV followed by MVA-BN-Filo) and later received a Ad26.ZEBOV booster dose approximately one year after dose 1 exhibited a strong anamnestic humoral response. HIV positive adult participants exhibited comparable humoral immune responses in these trials at the 21 days post-dose 2 (MVA-BN-Filo) time point, but the durability of these responses is unknown. It also remains to be determined what anamnestic response a booster dose with Ad26.ZEBOV would have in HIV positive individuals. The marketing authorisation approval under exceptional circumstances that was granted by the European Medicines Agency for the 2-dose Ebola vaccine regimen (Ad26.ZEBOV followed by MVA-BN-Filo) includes a recommendation for a boost dose with Ad26.ZEBOV in participants who received the 2-dose regimen at least four months previously in case of risk of exposure to EVD (7).

It is therefore important to elucidate the immunogenicity and safety of an Ad26.ZEBOV booster dose in HIV positive adult participants who previously received the 2-dose Ebola vaccine regimen. The findings of this trial could potentially inform future EVD-related public health interventions in HIV positive adults since they constitute an important population in regions at risk of EVD outbreaks.

2 OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1 OBJECTIVES AND ENDPOINTS To assess the safety and tolerability of a booster dose of Ad26.ZEBOV at a dose of $5x10^{10}$ vp in HIV positive adults previously vaccinated with Ad26.ZEBOV, MVA-BN-Filo vaccine regimen.

- 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 HIV positive adults previously vaccinated with the Ad26.ZEBOV,MVA-BN-Filo vaccine regimen.

2.2 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.

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 HIV positive adults who were previously vaccinated with Ad26.ZEBOV followed by MVA-BN-Filo 28 days or 56 days later in Africa. Only HIV-seropositive adults who received the 2-dose Ebola vaccine regimen during their participation in VAC52150EBL2002, the parent trial, are eligible for enrolment in this study. Approximately 50 subjects aged ≥ 18 to ≤50 years at randomisation in the parent VAC52150EBL2002 trial in Kenya and Uganda, will be enrolled to receive one booster dose of Ad26.ZEBOV approximately 4 years from the time they received dose 2 of the 2-dose Ebola vaccine regimen.

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).

Potential participants will be asked to provide informed consent to take part in the study.

After informed consent has 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, a full physical examination (including body height and weight), vital sign measurements, an HIV assessment (CD4+ T-cell count and viral load), a haematological assessment, and a urine pregnancy test for all females of childbearing potential at the time of screening and immediately prior to vaccination.

After vaccination, participants will remain under observation at the study site for at least 30 minutes for surveillance of any acute reactions and solicited events, or longer if deemed necessary by the investigator. In addition, participants will record solicited events in a diary for 7 days post-booster vaccination. Following the vaccination, any unsolicited, solicited local (at the injection site) or systemic AEs, and vital signs will be documented by study-site personnel at the end of this observation period.

The participant 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 the participant to document solicited local 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 participant feels warm to the touch. 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).

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

4 PARTICIPANT POPULATION

The study will be open to healthy (based on physical examination, medical history, and clinical judgement) HIV positive adults who received the Ad26.ZEBOV and MVA-BN-Filo vaccine regimen in the VAC52150EBL2002 trial, at sites in Kenya and Uganda. Potential participants should be virologically suppressed and immunologically controlled on their HAART regimen.

The inclusion and exclusion criteria for enrolling participants in this study are described in the following two sub-sections. 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. Must have previously received the 2-dose Ebola vaccine regimen at sites in Kenya or Uganda in **Cohort 2a** of the VAC52150EBL2002 study.
2. Must be a male or female subject and aged 18 - 50 years at time of randomisation in the parent trial (VAC52150EBL2002).
3. Must consent to participate in the study by signing (or thumbprinting, if illiterate) an ICF, indicating that he or she understands the purpose of, and procedures required for, the study, and he/she understands the potential risks and benefits of the study. If a potential participant 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 and documented.
4. Must be willing/able to ensure that they adhere to the prohibitions and restrictions specified in this protocol (see Section 4.3)
5. Must be available and willing to participate for the duration of the study visits.
6. Must be in reasonably good medical condition (absence of acquired immunodeficiency syndrome [AIDS]-defining illnesses or clinically significant disease), diagnosed on the basis of physical examination, medical history, and vital signs at screening, and the investigator's clinical judgement.
7. Must be on a stable regimen of HAART taking into account the following criteria:
    a. HAART is defined as potent anti-HIV treatment including a combination of ≥2 antiretroviral agents (ARVs; low-dose ritonavir does not count as an ARV) whose purpose is to reduce viral load to undetectable levels. Mono-therapy will not be allowed.
    b. HAART is considered stable if potential participants did not change their ARVs within the last 4 consecutive weeks prior to start of screening. Changes in formulations of the same drugs are allowed.
    c. A potential participant entering the study on HAART should have a HIV viral load of <50 copies/mL and a CD4+ T-cell count of >350 cells/µL at screening.
    d. The potential participant must be willing to continue his/her HAART throughout the study as directed by his/her local physician.
8. Potential participants must be healthy on the basis of clinical laboratory tests performed at screening. If the results of the laboratory screening tests are outside the institutional normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the investigator. However, the subject should not be included when haemoglobin is lower than the institutional normal reference range (or below the values in Attachment 1 when that range is not available).

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

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

9. Female subjects of childbearing potential must use adequate birth control measures consistent with local regulations regarding the use of birth control for subjects participating in clinical studies from at least 14 days before vaccination until the end of the study, with a negative urine beta human chorionic gonadotropin (β-hCG) pregnancy test at screening and immediately prior to the vaccination, which shall occur no earlier than 14 days after the screening visit.
10. Must have a means to be contacted

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 VAC52150EBL2002 trial who were in any study cohort other than cohort 2a, or were allocated to the placebo arm in Cohort 2a.
2. 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 (e.g. gentamicin).
3. 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 enrollment at that time but may be rescheduled for enrollment at a later date.
4. Women who are breast-feeding or known to be pregnant or planning to become pregnant while enrolled in the study or within 1 month after the booster vaccination. (A pregnancy test will be performed in woman of childbearing potential at screening and on vaccination day immediately before the vaccination).
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. Received a blood transfusion or other blood products within 8 weeks of enrolment.
7. Potential participants who have been vaccinated with live-attenuated vaccines within 30 days before and after the study vaccination, and with inactive vaccine within 15 days before and after the study vaccination.
8. Receipt of any disallowed therapies as noted in Section 7 before the planned administration of the vaccine on Day 1.
9. Subjects who, in the opinion of the investigator, are unlikely to adhere to the requirements of the study or are unlikely to complete the study.
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.

NOTE: Investigators should ensure that all study enrollment 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 that are clinically significant) after enrolment but before the vaccination is given (Day 1) such 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 participant must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. In case of a new Ebola outbreak: participants must not travel to an area with Ebola outbreak while the participant is enrolled in the study from the start of enrolment onwards until the last study visit. If applicable, any traveling to an area with Ebola outbreak should be documented in the case report form (CRF). The date of travel and the destination should be clearly identified.

2. For sexually active female subjects of childbearing potential, it should be confirmed that adequate birth control measures, consistent with what is available and the local standards regarding the use of birth control for subjects participating in clinical studies, were used from at least 14 days before the vaccination, with a negative urine β-hCG pregnancy test at screening and a negative urine β-hCG pregnancy test immediately prior to the study vaccination. If the pregnancy test result is positive, in order to maintain subject confidentiality, the investigator will ensure adequate counseling and follow-up will be made available. All females participants of non-childbearing potential, will be asked to use adequate birth control for sexual intercourse until at least 28 days after the vaccination. The sponsor considers the following methods of birth control to be highly effective: established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; barrier methods (condom or occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository); male partner sterilisation (the vasectomised partner should be the sole partner for that subject). More restrictive measures may be required by the site. Abstinence or natural family planning are not acceptable birth control methods.

   Women are considered not of childbearing potential if they are postmenopausal (>45 years of age with amenorrhea for at least 2 years or ≤ 45 years of age with amenorrhea for at least 6 months and a serum follicle stimulating hormone (FSH) level > 40 mIU/mL); permanently sterilised (e.g., bilateral tubal occlusion [which includes tubal ligation procedures as consistent with local regulations], hysterectomy, bilateral salpingectomy, bilateral oophorectomy); or otherwise be incapable of pregnancy. Women aged ≤ 45 years with amenorrhea for ≤6 months are considered of childbearing potential and do not need FSH testing.

   Note: If the social situation of a woman changes after start of the study (e.g. woman who is not heterosexually active becomes active), she must begin a highly effective method of birth control, as described above.

3. Ensure that they do not use any disallowed concomitant therapies 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 mL IM injection into the anterolateral 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 0.5 mL IM injections in the anterolateral deltoid, 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 anesthetic 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 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 recognise and treat anaphylaxis must be present in the clinic during the entire vaccination procedure and post-vaccination monitoring period.

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

The Site Investigational Product Procedures Manual specifies the procedures for administration of the study intervention.

Ad26.ZEBOV will be manufactured under the responsibility of Janssen Vaccines & Prevention B.V. It will be labelled and packaged under the responsibility of the sponsor. Please refer to the IB and addenda (if applicable) for a list of excipients (2).

6.1 CRITERIA FOR POSTPONEMENT OF VACCINATION

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

- Acute illness at the time of vaccination (this does not include minor illnesses such as diarrhoea or mild upper respiratory tract infection);
- 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 must be recorded in the CRF from screening onwards until 28 days post-vaccination (Day 29).

All uses of HAART should be recorded as concomitant therapy. Information on concomitant use of herbal supplements or vitamins will not be collected.

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 immunisations or the interpretation of immune responses to study intervention, as well as to avoid potential confusion with regard to attribution of adverse reactions. For live-attenuated vaccines, the required period is 30 days. However, if a vaccine is indicated in a post-exposure setting (e.g., rabies or tetanus), it must take priority over the study intervention.

Analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs may be used post-vaccination in case of medical need (e.g., fever ≥38.0°C or pain). The use of these medications must be documented. Use of these medications as routine prophylaxis prior to study intervention administration is prohibited.

Chronic or recurrent use of medications that modify the host immune response (e.g., cancer chemotherapeutic agents, systemic corticosteroids, immunomodulators) are prohibited. 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 must have signed a study ICF (see Section 15.2 Informed 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

Approximately 10 mL of blood will be drawn from participants at each blood draw, with an additional 2 mL at the screening visit, for a cumulative total of 42 mL over the study period. This volume remains well below the limits of standard blood donation.

For details on the approximate blood sampling volumes collected by visit and the cumulative blood volumes, refer to the TIME AND EVENTS SCHEDULE.

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

8.1.2 Screening Period

Up to 28 days before Day 1 (day of vaccination) and after signing and dating the ICF (see Section 15.2.3), screening assessments will be performed as indicated in the TIME AND EVENTS SCHEDULE. Screening may be split into multiple days or visits.

Only subjects 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 subject, and will obtain the subject's written informed consent prior to study participation.

If the site decides to use a Test of Understanding (TOU) for the consenting process, it should be administered after reading but before signing the ICF. If the subject fails the TOU, he/she may repeat the test twice (and have to pass the third time to be eligible) (for details, see Section 15.1).

The overall eligibility of the subject to participate in the study will be assessed once all screening values and results of any other required evaluations are available. Retesting of values that lead to exclusion is allowed once using an unscheduled visit during enrolment to assess eligibility. If rescreening is required, all screening procedures (except TOU, if applicable) should be repeated. 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 Day 1, to serve as pre-vaccination baseline sample for immunogenicity assessments (see Section 8.4).

8.1.3 Vaccination Period

If eligible, the participant will come for the vaccination visit (Day 1). The investigator should ensure that all screening 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 be excluded from further participation in the study.

Before vaccination, a brief symptom-directed 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 participant will be provided with a thermometer (to measure body temperature), a ruler (to measure local injection site reactions), and a participant diary to record body temperature and solicited local (at injection site) and systemic symptoms and will be trained on how to collect this information. Symptoms of solicited local and systemic 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 the participant daily. The investigator or clinical designee will review information from the participant's diary.

Participants will return to the site as indicated in the TIME AND EVENTS SCHEDULE. 7 days after vaccination (Day 8). The participant's diary will be reviewed and completed by study-site personnel. The investigator will examine the injection site for occurrences of erythema, swelling, or tenderness at this visit in order to complete the Day 8 section of the diary as well as the relevant parts of the CRF.

Unsolicited AEs will be reported from the first day of 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 the end of the study.

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

The final study visit at 28 days after vaccination (Day 29) will be used to assess safety only. Participants will be given the option to conduct this visit in-person at the clinic or over the phone.

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 available 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, if applicable]). Participants that are rescreened due to a pause must have new assessments (including physical examination and vital signs) within 28 days of the booster vaccination. If applicable, 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 investigators, 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 regular review of the safety data during the study. Details regarding this role are provided in Section 10.7.

Symptoms of solicited local (at the injection site) 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 Adverse Event section of the CRF.

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

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

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 (at the injection site) 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 the participant on the day of vaccination (Day 1) and daily for the next 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 into 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

Participants will be asked to note in the diary occurrences of tenderness, erythema and swelling at the study intervention injection site on the day of vaccination and daily for 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 localised at the injection site upon palpation or movement of the limb. Due to subjective nature of the reaction, the severity assessment of tenderness is self-reported (if a participant is unable to provide self-report, other reporters include 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 localised 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 injection. It may be either soft (typically) or firm (less typical).

- **Itching**

  This refers to the local itching at the site of injection.

  <u>Note</u>: Any other injection site events not meeting the above case definitions should be reported separately as unsolicited AEs.

Solicited Systemic Adverse Events

The participant will be instructed on how to record daily temperature using a thermometer provided for home use. The body 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.

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

The participant will also be instructed on how to note daily (day of vaccination and the subsequent 6 days) the following symptoms or events:

- body temperature
- fatigue/malaise
- chills
- headache
- nausea/vomiting
- muscle pain
- joint pain

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

Physical Examination

At screening, a full physical examination, including body weight and height, will be conducted. At subsequent visits, a brief, symptom-directed examination will be performed based on 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 adverse event.

Vital Signs

Body 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

An HIV assessment (CD4+ T-cell count and viral load) and a haematological assessment (full blood count) will be performed by the local laboratory at screening (see TIME AND EVENTS SCHEDULE). The investigator must review the laboratory report, document this review, and record any clinically relevant values on the screening page of the CRF. Laboratory reports must be filed with the source documents.

Approximate blood volume expected to be drawn at screening for clinical laboratory assessments:

- 10 mL will be taken for monitoring of CD4+ T-cell count and HIV viral load
- 2 mL will be taken for the haematological baseline assessment. The following tests will be performed by the local laboratory, unless otherwise specified:
    - Haematology Panel
        - haemoglobin
        - haematocrit

- red blood cell count
- white blood cell count with differential
- platelet count

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 monitor 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 this study and the sponsor's medical monitor will be notified immediately:

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

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

2. One or more participants experience an SAE (solicited or unsolicited) that is determined to be related to study intervention; *OR*
3. One or more participants experience anaphylaxis or generalised urticaria within 24 hours of vaccination, clearly not attributable to other causes than vaccination with 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 designee immediately and no later than 24 hours 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 designee 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, 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)/Institutional Review Board (IRB) 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 shipped to Q2 Solutions laboratory for analysis of binding antibodies against EBOV GP using the FANG ELISA.

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 the host countries 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 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 participant has the right to withdraw from the study at any time for any reason. The investigator should make an attempt to contact participants who did not return for scheduled visits. Although a participant is 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 investigators to stop or cancel the study

- Decision by local regulatory authorities or IEC/IRB to stop or cancel the study

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

When a participant withdraws before completing the study, the reason for withdrawal, if given, is to be documented in the CRF and in the source document.

A participant who wishes to withdraw consent will be offered an optional visit for safety follow-up (before the formal withdrawal of consent). The participant has the right to refuse this optional visit.

Withdrawal of Consent for the Use of Samples in Future Research

A participant may withdraw consent for 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 analyse 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 HIV positive adult participants are expected to be enrolled into this trial. This number is based on the potentially available HIV positive participants who previously received the 2-dose Ebola vaccine regimen (Ad26.ZEBOV followed by MVA-BN-Filo) at sites in Kenya and Uganda.

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 summarised 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 summarised.

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 serious adverse event.

Physical Examination

Because only abbreviated, symptom-directed examinations are performed per 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 summarised at each scheduled time point. A listing of participants with clinically significant abnormal values will be provided.

10.5 IMMUNOGENICITY ANALYSIS

Graphical representations of immunological parameters will be made as applicable. Frequency tabulations will be calculated for discrete (qualitative) immunologic parameters as applicable.

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 HIV positive adults in previous studies. A booster dose of Ad26.ZEBOV was also shown to be safe in HIV negative 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 8.3.2) or in any situation that could affect the safety of the participants.

After the review, the independent medical reviewer will make recommendations regarding the continuation of the 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 will be conducted in accordance with those procedures.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant 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 is specifically questioned, and which are noted in the participant's diary.

Unsolicited Adverse Events

Unsolicited AEs are all adverse events for which the participant 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 time period of sponsor's adverse event collection, see Section 11.3.

Serious Adverse Event

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

- Results in death
- Is life-threatening (the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient 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 hospitalisation but may jeopardise 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 them).

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.

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.

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

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.

11.1.3 Severity Criteria

All AEs, except for solicited AEs, will be coded for severity using a modified version of the United States National Institutes of Health, Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.1, July 2017).

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

Mild	Grade 1	Symptoms causing no or minimal interference with usual social and functional activities.
Moderate	Grade 2	Symptoms causing greater than minimal interference with usual social and functional activities.
Severe	Grade 3	Symptoms causing inability to perform usual social and functional activities.

Note: Grade 3 AEs include life-threatening events and deaths related to the AE.

Note: Only clinically significant abnormalities in laboratory data occurring from signing of the ICF onwards will be reported as AEs and graded using the DAIDS Table.

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 an 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.

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 AEs 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 11.1.2.

The investigator or clinical designee must review both post-injection reactogenicity and other adverse event CRFs to insure the prompt and complete identification of all events that require expedited reporting as 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 etiology (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 where required) all SUSARs. The investigator (or sponsor as required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB.

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

The participant will be provided with a "participant identification card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Site number
- Participant name or photograph

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 the IEC/IRB as required.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours and to the IEC/IRB as required. The initial and follow-up reports of an SAE should be 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 stabilises
- 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 an 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 an 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 long-term care facility)
- Surgery or procedure planned before entry into the study (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 serious adverse events. 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 serious adverse event.

11.2.3 Pregnancy

Female participants who are pregnant at screening will be excluded. Enrolled study participants who become pregnant during the study will be followed up as per protocol.

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 an SAE, the study-site personnel must report the PQC to the sponsor according to the serious adverse event 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 Vaccine & 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 to the sites as a separate document.

13 STUDY INTERVENTION INFORMATION

13.1 AD26.ZEBOV

Ad26.ZEBOV is a monovalent, replication-incompetent adenovirus serotype 26-based vector that encodes 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 [2,3]

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

13.2 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 relabeled without prior approval from the sponsor.

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

13.3 LABELLING

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

13.4 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 unauthorised 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 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.

13.5 INTERVENTION ACCOUNTABILITY

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

Study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention must be available for verification by the sponsor's study site monitor during on-site monitoring visits. Once the study sponsor has given its authorisation, study intervention supplies are destroyed on-site according to local regulations. 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 sites agreed upon with the sponsor.

14 STUDY -SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure 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(s)
- Participant diaries
- TOU
- Rulers, thermometers
- Participant identification cards

15 ETHICAL ASPECTS

15.1 STUDY-SPECIFIC DESIGN CONSIDERATIONS

Potential participants 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. Potential participants will be fully informed of the risks and requirements of the study. During the study, participants 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 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 enroll in the study.

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

Test of Understanding (if applicable)

The TOU is a short assessment of the potential participant's understanding of key aspects of the study. The test will help the study staff to determine how well the potential participant understands the study and the requirements for participation.

The potential participant 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 potential participant. The potential participant must subsequently sign the ICF, indicating that he or she is willing to participate in the study.

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

Any potential participant not capable of understanding the key aspects of the study, and their requirements for participation, should not be allowed to enroll in the study.

15.2 REGULATORY ETHICS COMPLIANCE

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 or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF(s) (and any other written materials to be provided to the study subjects, e.g., participant diary)
- Investigator's Brochure and amendments/addenda
- 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/IRB)
- 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/IRB requests to fulfil its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for 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/IRB and the documents being approved.

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data, or study conduct)
- Revision(s) to ICF(s), 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/IRB (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/IRB

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(s) revisions will be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

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

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

15.2.3 Informed Consent

Consent at the Individual Level

Each subject (potential participant) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF must be signed or thumb-printed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorised member of the study-site personnel must explain to the subject the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. The subject will be informed that their participation 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 authorised sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorising such access, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact them for the purpose of obtaining consent for additional safety evaluations.

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

If the subject 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 in a language that the participant understands). The impartial witness should personally date and sign the ICF after the consent of the subject is obtained.

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 organisational measures to protect the personal data against unauthorised 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 participant includes explicit consent for the processing of personal data of the participant and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to their personal data 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 participants. 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 participants 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 Kenya, Uganda, and neighbouring countries. This may include the development of new or the improvement of existing techniques to characterise EBOV-directed immune responses or diagnostic tests. No additional samples will be taken for these analyses, however, residual samples from study tests may be retained for these purposes and analysed after the end of the study.

Participants will be asked to consent voluntarily for their 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. Participants may withdraw consent for their 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/IRB 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/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB will be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB/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 authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

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/IRB approval of the protocol, amendments, ICF(s), 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/IRB, including a current list of the IEC/IRB 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/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification
- 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 enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

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

The investigator must also complete a participant screening log, which reports on all participants who were seen to determine eligibility for inclusion in the 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 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, if applicable, and the 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, vital signs) 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 authorised study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF (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 CRF, this can be done in either of the following ways:

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

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 body. 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 16.2, 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 standard operating procedures.

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 enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the vaccination unit and/or clinic records (source documents) (eg, hospital / clinic / physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In 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

16.9.1 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.

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

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

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) 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 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.

REFERENCES

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4. Ishola David MD, Afolabi Muhammed O., et al. Safety and long-term immunogenicity of a two-dose Ad26.ZEBOV, MVA-BN-Filo Ebola vaccine regimen in adults: a randomised trial initiated during the Ebola outbreak in Sierra Leone. Lancet Infect Dis. 2020;(submitted).
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6. Vaccine against Ebola: Commission grants new market authorisations [press release]. https://ec.europa.eu/commission/presscorner/detail/en/ip_20_1248, 1 July 2020 2020.
7. European Medicines Agency (EMA). Ervebo, Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP, live). Available at: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/ervebo. Accessed 17 December 2019.

ATTACHMENT 1: HAEMOGLOBIN CUT-OFF VALUES

Where no institutional normal reference ranges is available for haemoglobin, the following cut-off values are proposed. It is imperative to note that there are no standard accepted normative values for haemoglobin in most African countries and therefore, the following recommendations are based on the review of several published sources and in consultation with the sites involved with the study.

Group	Value (g/dL)		Reference
Adult and HIV+	Male 12.1	Female 9.5	Lower limit of normal (LLN) value for local sites in Kenya and Uganda, values being used in EBOVAC Phase 1 trials.

INVESTIGATOR AGREEMENT

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

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

Chief Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor Representative:

Name (typed or printed): _____

Institution: London School of Hygiene and Tropical Medicine

Signature: _____ Date: _____

(Day Month Year)

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