Janssen Vaccines & Prevention B.V. *

Clinical Protocol

A Multi-country, Prospective, Clinical Safety Study of Subjects Exposed to the Candidate Ebola Vaccines Ad26.ZEBOV and/or MVA-BN-Filo

Protocol VAC52150EBL4001; Phase 3
AMENDMENT 2

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

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

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	25-Nov-2015
Amendment 1	30-Sep-2016
Amendment 2	This document

Amendments below are listed beginning with the most recent amendment.

Amendment_2 (this document)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: Originally, all subjects who were exposed to Ad26.ZEBOV and/or MVA-BN-Filo in a Phase 1, 2 or 3 clinical study were to be approached to consent for enrollment into the VAC52150EBL4001 study. With this amendment, this will no longer be the case. Each local authority will determine which cohorts will be opened for enrollment in their region. It is not mandatory to open all cohorts for enrollment. As a result, a local authority may restrict enrollment to 1 or 2 cohorts, rather than allowing enrollment in all cohorts.

The original development plan (at the time of the ongoing Ebola epidemic in Africa) was an accelerated plan with the anticipation of conducting Phase 3 efficacy studies (with limited safety data collection) shortly after Phase 1 and in parallel with Phase 2. The sponsor designed the VAC52150EBL4001 study for the extended follow-up of serious adverse events (SAEs) to enhance the ability for signal detection of rare events. Since there is no longer an ongoing Ebola epidemic, it is not currently possible to conduct a parallel Phase 3 efficacy study as part of an accelerated development plan. More controlled safety data will become available for all vaccinated subjects, therefore, prior to any potential future efficacy study.

The changes made to the clinical protocol VAC52150EBL4001 are listed below, including the rationale of each change and a list of all applicable sections.

Rationale: It was specified that each local authority will determine which cohorts will be opened for enrollment in their region. It is not mandatory to open all cohorts for enrollment. As a result, a local authority may restrict enrollment to 1 or 2 cohorts, rather than allowing enrollment in all cohorts. The approximate number of subjects potentially to be enrolled in this study was updated.

SYNOPSIS

3.1 Overview of Study Design

5 SUBJECT POPULATION

5.1 Inclusion Criteria

11.2 Sample Size Determination

Rationale: Updates were made to the Background section and references were added to the latest versions of the Investigator's Brochure of Ad26.ZEBOV and MVA-BN-Filo. In addition, the potential risk of myo/pericarditis was removed because no cardiovascular events were associated with the current MVA-BN-Filo vaccine.

1.1 Background

1.2 Benefit/Risk Section

1.2.4 Potential Risks

REFERENCES

Rationale: Minor editorial changes have been made throughout the document.

1.1 Background

5.1 Inclusion Criteria

Amendment_1 (30 September 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: Since validated assays are not available yet to assess immune responses in the ongoing Phase 2 and 3 studies, unblinding of these studies has been delayed. Therefore, subjects who received placebo in their original Phase 2 or 3 study will also be approached for enrollment into the VAC52150 Vaccine Development Roll-over study before unblinding of their original study.

The changes made to the clinical protocol VAC52150EBL4001 are listed below, including the rationale of each change and a list of all applicable sections.

Rationale: Unblinding of the ongoing Phase 2 and 3 studies has been delayed. Therefore, placebo subjects from these studies who reach the last study visit before unblinding of their original study, will be approached for enrollment into the VAC52150 roll-over study. Details on the procedures for these subjects have been added.

SYNOPSIS

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11.2 Sample Size Determination

11.4 Subject Information

11.5 Safety Analyses

12.3.2 Pregnancy

Rationale: Safety information following MVA-BN-Filo vaccine administration based on the pooled safety data from studies VAC52150EBL1001 and VAC52150EBL1002 has been included.

1.1 Background

1.2.3 Known Risks

1.2.4 Potential Risks

Rationale: Based on the request of the Food and Drug Administration, the study phase is updated to Phase 3.

Title Page

Rationale: Name change from Crucell Holland B.V. to Janssen Vaccines & Prevention B.V.

Title Page

1 INTRODUCTION

REFERENCES

INVESTIGATOR AGREEMENT

Rationale: Minor textual changes have been made, in addition to modifications for clarity and updates to be in line with other current protocols and the current Investigator Brochures.

SYNOPSIS

1 INTRODUCTION

5 SUBJECT POPULATION

SYNOPSIS

A Multi-country, Prospective, Clinical Safety Study of Subjects Exposed to the Candidate Ebola Vaccines Ad26.ZEBOV and/or MVA-BN-Filo

The sponsor, in collaboration with Bavarian Nordic GmbH (BN), is investigating the potential of a prophylactic Ebola vaccine regimen comprised of the following 2 candidate Ebola vaccines:

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

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

The EBOV GP that circulated in West Africa has 97% homology to the EBOV GP used in these vaccine regimens.

Ad26.ZEBOV and MVA-BN-Filo are being evaluated in Phase 1, 2 and 3 clinical studies, in different heterologous prime-boost regimens, in which one study vaccine is used to prime a filovirus-specific immune response and the other study vaccine is used to boost the immune response. Homologous regimens for each vaccine are also being evaluated.

OBJECTIVES AND HYPOTHESIS

Objectives

The study objectives are:

- To collect serious adverse event information from subjects exposed to Ad26.ZEBOV and/or MVA-BN-Filo in a Phase 1, 2, or 3 clinical study, for a total of 60 months after prime vaccination (including the duration in the subject's original study).
- To collect pregnancy outcomes (including spontaneous/elective abortion, intrauterine death/stillbirth, information on delivery) and serious adverse event information during pregnancy from female subjects who became pregnant with estimated conception within 28 days after vaccination with MVA-BN-Filo or within 3 months after vaccination with Ad26.ZEBOV in a Phase 1, 2 or 3 clinical study.
- To collect serious adverse event information for up to 60 months after birth from children born to female subjects who became pregnant with estimated conception within 28 days after vaccination with MVA-BN-Filo or within 3 months after vaccination with Ad26.ZEBOV in a Phase 1, 2 or 3 clinical study.

Hypothesis

This is a descriptive study to document the long-term safety profile of Ad26.ZEBOV and MVA-BN-Filo and to address gaps in the currently available data for the risks of Ad26.ZEBOV and/or MVA-BN-Filo. As this study aims to describe the data for benefit-risk assessment purposes, no hypotheses are pre-specified.

OVERVIEW OF STUDY DESIGN

This is a multi-country, prospective, long-term clinical safety study designed to extend the total follow-up period of vaccinated subjects up to 60 months (including the duration in the subject's original study), to allow collection of serious adverse events and pregnancy outcomes (including spontaneous/elective abortion, intrauterine death/stillbirth, information on delivery) following administration of Ad26.ZEBOV and/or MVA-BN-Filo for the prevention of Ebola virus disease among subjects who participated in a Phase 1, 2 or 3 clinical study. In addition, offspring from vaccinated female subjects who became pregnant with estimated conception within 28 days after vaccination with MVA-BN-Filo or within 3 months after vaccination with Ad26.ZEBOV in a Phase 1, 2 or 3 clinical study will be followed up to 60 months after birth. Up to approximately 3,000 subjects may potentially be enrolled in this study, based on the number of exposed subjects in the contributing Phase 1, 2 or 3 clinical studies.

Since validated assays are not available yet to assess immune responses in the ongoing Phase 2 and 3 studies, unblinding of these studies has been delayed. Therefore, subjects in the ongoing Phase 2 and 3 studies who reach the last study visit will be approached to consent for enrollment into the VAC52150 Vaccine Development Roll-over study for long-term safety surveillance (for a total of up to 60 months after the prime vaccination). After unblinding of their original study only subjects who received Ad26.ZEBOV and/or MVA-BN-Filo will remain in this VAC52150 Vaccine Development Roll-over study for long-term safety surveillance. After unblinding, subjects who received placebo and have already been enrolled into the VAC52150 Vaccine Development Roll-over study will be discontinued from further participation in this roll-over study. This also applies to pregnant subjects who received placebo (ie, subjects enrolled in Cohort 2) or offspring from vaccinated female subjects who received placebo (ie, subjects enrolled in Cohort 3).

The study will consist of an enrollment visit, a number of follow-up contacts and an end-of-study contact. These contacts are preferably conducted by phone; if not possible, a study site visit needs to be organized. Preferably, offspring from vaccinated female subjects will visit the study site for every study visit. If not possible, the child may be visited at home by study site staff or a qualified health care worker for data collection.

Data collection can start when a signed informed consent form (ICF) is available for the current study. Preferably, signing of the ICF occurs at the last visit of the subject's original study (or at birth for offspring). If this is not possible, baseline data will be collected when a signed ICF is available and data need to be captured retrospectively up to the moment of enrollment in the current study.

Data collection will be as follows for the 3 cohorts:

Cohort 1: Data for subjects vaccinated with Ad26.ZEBOV and/or MVA-BN-Filo (or placebo) in a Phase 1, 2 or 3 clinical study (adults, adolescents and children) and who consent to participation in the current study will be collected in 6-month intervals. Data collection will continue for a total of 60 months after prime vaccination (including the duration in the subject's original study).

Cohort 2: Data on the pregnancy outcome of female subjects who became pregnant with estimated conception within 28 days after vaccination with MVA-BN-Filo (or placebo) or within 3 months after vaccination with Ad26.ZEBOV (or placebo) in a Phase 1, 2 or 3 clinical study and who consent to participation in the current study will be collected at notification of the pregnancy, and at the end of the pregnancy. These subjects will be followed in Cohort 2 up to the end of their pregnancy. Thereafter, female subjects will continue to be followed in Cohort 1 (to reach a total of 60 months follow-up after prime vaccination including the duration in the subject's original study); live-born children will be followed in Cohort 3.

Cohort 3: Data for children born to female subjects exposed to Ad26.ZEBOV and/or MVA-BN-Filo (or placebo) in a Phase 1, 2 or 3 clinical study who became pregnant with estimated conception within 28 days after vaccination with MVA-BN-Filo (or placebo) or within 3 months after vaccination with

Ad26.ZEBOV (or placebo) and for whom consent for the current study is given, will be collected in 6-month intervals, and up to 60 months after birth.

Each local authority will determine which cohorts will be opened for enrollment in their region. It is not mandatory to open all cohorts for enrollment. As a result, a local authority may restrict enrollment to 1 or 2 cohorts, rather than allowing enrollment in all cohorts.

After unblinding of their original study, subjects from Cohort 1 and 2 who received placebo or offspring (Cohort 3) from female subjects who received placebo will be discontinued from further participation in this roll-over study.

SUBJECT POPULATION

The study will be open to subjects who participated in a Phase 1, 2 or 3 clinical study with Ad26.ZEBOV and/or MVA-BN-Filo and who received at least one dose of study vaccine (active vaccine or placebo).

SAFETY EVALUATIONS

Serious adverse event information in each cohort, pregnancy outcomes (including spontaneous/elective abortion, intrauterine death/stillbirth, information on delivery) and growth measurements for offspring will be collected.

STATISTICAL METHODS

There are no planned interim analyses. However, the accumulating data during study conduct may be used for reporting required for health authority submissions or other purposes. As this is a non-comparative study without formal hypotheses, any interim data may be used for purely administrative purposes without having an impact on study conduct or need for statistical adjustments. All interim reporting must be approved by the study responsible physician and project statistician prior to conduct.

No formal statistical testing of safety data is planned. Incidence rates of serious adverse events in each cohort, of pregnancy overall and by pregnancy outcome (including spontaneous/elective abortion, intrauterine death/stillbirth, information on delivery) will be calculated for all events and the number of events per person-year (where applicable), with corresponding 2-sided 95% confidence intervals. Incidence rates will also be tabulated by age group.

Results for subjects who received active vaccine or placebo will be presented separately.

TIME AND EVENTS SCHEDULE

1. COHORT 1: VACCINATED SUBJECTS

Data collection schedule for subjects exposed to Ad26.ZEBOV and/or MVA-BN-Filo (or placebo) in a Phase 1, 2 or 3 clinical study:

	Visit 1[a]	Contact 2[a]	Subsequent Contacts[a]	End of Study[a]
	Baseline (Start of Data Collection)[b]	**Month 6**	**Every 6 Months**	**After 60 Months of Follow-up[c]**
Subject information				
Subject consent[d]	X			
Selection criteria	X			
Demographics[e]	X			
Ongoing subject review				
Serious adverse events[e,f]	X	X	X	X
Medication and vaccinations[e,g]	X	X	X	X
Study completion/withdrawal				
End-of-study form				X[h]

a. Only the first visit is a study site visit (and may coincide with the last visit in the subject's original study); data collection at other time points will preferably occur through phone calls. If not possible by phone, a study site visit needs to be organized.
b. Data collection can start when a signed informed consent form (ICF) is available for the current study. Preferably, this occurs at the last visit of the subject's original study. If this is not possible, baseline data will be collected when a signed ICF is available and data will be captured retrospectively from the subject's last visit in the original study up to the moment of enrollment in the current study.
c. The subject should be followed for a total of 60 months after prime vaccination, including the duration in the subject's original study.
d. Before the start of data collection in this study, all subjects and/or their legally-acceptable representative (where applicable) must sign an ICF for the current study indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.
e. Relevant data will be copied from the analysis data set of the subject's original study. Any relevant new information should be added in the Case Report Form (CRF) of the current study.
f. All serious adverse events are to be documented for a total of 60 months after prime vaccination (including the duration in the subject's original study).
g. Any medication taken within a period of 30 days prior to the onset of a serious adverse event and up to the resolution of the serious adverse event.
h. When an enrolled subject completes or withdraws from the study, or is lost to follow-up, the investigator will complete the end-of-study form for the individual subject and provide a specific date for the end-of-study observation(s).

2. COHORT 2: PREGNANCY OUTCOMES

Data collection schedule for female subjects who became pregnant with estimated conception within 28 days after vaccination with MVA-BN-Filo (or placebo) or within 3 months after vaccination with Ad26.ZEBOV (or placebo) in a Phase 1, 2, or 3 clinical study:

	Visit 1[a]	End of Pregnancy Follow-up[a]
	Baseline (Start of Data Collection)[b]	**End of Pregnancy**
Subject information		
Subject consent[c]	X	
Selection criteria	X	
Demographics[d]	X	
Ongoing subject review		
Serious adverse events[d,e]	X	X
Medication and vaccinations[d,f]	X	X
Pregnancy follow-up[g]	X	X
Study completion/withdrawal		
Transition to Cohort 1[h]		X[i]

a. Only the first visit is a study site visit; data collection at the end of the pregnancy will preferably occur through a phone call. If not possible by phone, a study site visit needs to be organized.
b. Data collection can start when a signed ICF is available for the current study. Preferably, this occurs at the last visit of the subject's original study. If this is not possible, baseline data will be collected when a signed ICF is available and data will be captured retrospectively from the subject's last visit in the original study up to the moment of enrollment in the current study.
c. Before the start of data collection in this study, all subjects and/or their legally-acceptable representative (where applicable) must sign an ICF for the current study indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.
d. Relevant data will be copied from the analysis data set of the subject's original study. Any relevant new information should be added in the CRF of the current study.
e. All serious adverse events in subjects exposed to Ad26.ZEBOV (or placebo) and/or MVA-BN-Filo (or placebo) are to be documented. Data collection should start with study enrollment and continue until the end of the pregnancy.
f. Any medication taken within a period of 30 days prior to the onset of a serious adverse event and up to the resolution of the serious adverse event.
g. Information on obstetric history, maternal/paternal risk factors, pregnancy outcome (including spontaneous/elective abortion, intrauterine death/stillbirth, information on delivery).
h. After the pregnancy, female subjects will continue to be followed up in Cohort 1. A live-born child will be followed up in Cohort 3.
i. When an enrolled subject completes or withdraws from the study, or is lost to follow-up, the investigator will complete the end-of-study form for the individual subject and provide a specific date for the end-of-study observation(s).

3. COHORT 3: OFFSPRING

Data collection schedule for children born to female subjects who became pregnant with estimated conception within 28 days after vaccination with MVA-BN-Filo (or placebo) or within 3 months after vaccination with Ad26.ZEBOV (or placebo) in a Phase 1, 2, or 3 clinical study:

	Visit 1[a]	Visit 2[a]	Subsequent Visits[a]	End of Study[a]
	Baseline (Start of Data Collection)[b]	Month 6	Every 6 Months	60 Months After Birth
Subject information				
Subject consent[c]	X			
Selection criteria	X			
Demographics	X			
Medical history[d]	X			
Ongoing subject review				
Serious adverse events[e]	X	X	X	X
Medication and vaccinations[f]	X	X	X	X
Growth measurements[g]	X	X	X	X
Study completion/withdrawal				
End-of-study form				X[h]

a. Preferably, offspring from vaccinated female subjects will visit the study site for every study visit. If not possible, the child may be visited at home by study site staff or a qualified health care worker for data collection.
b. Data collection can start when a signed ICF is available for the current study (at birth or as soon as possible after birth). If this is not possible, baseline data will be collected when a signed ICF is available and data will be captured retrospectively from birth up to the moment of enrollment in the current study.
c. Before the start of data collection in this study, the subject's parent or legally-acceptable representative (where applicable) must sign an ICF for the current study indicating that he or she understands the purpose of and procedures required for the study and is willing to let their child participate in the study.
d. Medical history of the child may include information on birth (preterm/full term), presence of birth defects, medical interventions beyond routine interventions at birth and relevant information from the mother's pregnancy follow-up, family history of growth (details on stature of parents and siblings).
e. All serious adverse events are to be documented. Data collection should start with the time of birth and continue for 60 months.
f. Any medication taken within a period of 30 days prior to the onset of a serious adverse event and up to the resolution of the serious adverse event.
g. Height, weight, growth percentiles.
h. When an enrolled subject completes or withdraws from the study, or is lost to follow-up, the investigator will complete the end-of-study form for the individual subject and provide a specific date for the end-of-study observation(s).

ABBREVIATIONS

Ad26	adenovirus serotype 26
Ad26.ZEBOV	Ad26 vector expressing the glycoprotein of the Ebola virus Mayinga variant
AIDS	acquired immunodeficiency syndrome
BN	Bavarian Nordic
CRF	Case Report Form
EBOV	Ebola virus
eDC	Electronic Data Collection
EU	European Union
GCP	Good Clinical Practice
GP	glycoprotein
HIV	human immunodeficiency virus
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IM	intramuscular(ly)
IRB	Institutional Review Board
MARV	Marburg virus
MVA	Modified Vaccinia Ankara
MVA-BN-Filo	Modified Vaccinia Ankara Bavarian Nordic vector expressing multiple filovirus proteins
NHP	non-human primates
NP	nucleoprotein
PCR	polymerase chain reaction
RNA	ribonucleic acid
SUDV	Sudan virus
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAFV	Tai Forest Virus
$TCID_{50}$	tissue culture infective dose
US	United States
VISP	vaccine induced seropositivity
vp	viral particles
WHO	World Health Organization

1. INTRODUCTION

Janssen Vaccines & Prevention B.V. (formerly known as Crucell Holland B.V., hereafter referred to as the sponsor), in collaboration with Bavarian Nordic GmbH (BN), is investigating the potential of a prophylactic Ebola vaccine regimen comprised of the following 2 candidate Ebola vaccines:

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

MVA-mBN226B, further referred to as Modified Vaccinia Ankara (MVA)-BN-Filo®, is a multivalent vaccine expressing the Sudan virus (SUDV) GP, the EBOV GP, the Marburg virus (MARV) Musoke GP, and the Tai Forest virus (TAFV, formerly known as *Côte d'Ivoire ebolavirus*) nucleoprotein (NP), 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 EBOV GP that circulated in West Africa has 97% homology to the EBOV GP used in these vaccine regimens.

Ad26.ZEBOV and MVA-BN-Filo are being evaluated in Phase 1, 2 and 3 clinical studies, as a heterologous prime-boost regimen that is administered in different sequences and schedules, in which one study vaccine is used to prime a filovirus-specific immune response and the other study vaccine is used to boost the immune response.

For the most up-to-date nonclinical and clinical information regarding Ad6.ZEBOV and MVA-BN-Filo, refer to the latest versions of the Investigator's Brochures and Addenda (if applicable).[5,6] A brief summary of the nonclinical and clinical information is provided below.

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

1.1. Background

Ebola viruses belong to the *Filoviridae* family and cause Ebola virus disease, which can induce severe hemorrhagic fever in humans and non-human primates (NHPs). Case fatality rates in Ebola virus disease range from 25% to 90% (average: 50%), according to the World Health Organization (WHO).[10] These viruses are highly prioritized by the United States (US) Government, who has defined them as 'Category A' agents, due to the high mortality rate of infected individuals. Currently, no licensed vaccine, treatment or cure exists for this disease.

Filoviruses are named for their long, filamentous shape. Within this filamentous virus, a single 19-kilobase (kb) negative-sense ribonucleic acid (RNA) genome encodes 7 proteins: the GP, the polymerase, the NP, the secondary matrix protein, the transcriptional activator, the polymerase cofactor, and the matrix protein. The virion surface is covered by homotrimers of the viral GP, which is believed to be the sole host attachment factor for filoviruses. Following cell entry, the

viruses replicate their genomes and viral proteins in the cytoplasm using an RNA-dependent RNA polymerase, which is carried into the cell together with the virus.[3]

Nonclinical Studies

Immunogenicity and Efficacy

Immunogenicity and efficacy of the vaccine combination Ad26.ZEBOV and MVA-BN-Filo was evaluated in an NHP model (ie, Cynomolgus macaques, *Macaca fascicularis*). The combination was assessed in a multivalent filovirus setting in a small number (2 per regimen) of animals and the study included heterologous prime-boost regimens of adenovirus serotype 26 (Ad26), Ad35 and MVA-BN-Filo vectors expressing different Ebola and Marburg proteins. Full protection from Ebola virus disease and death after wild-type EBOV Kikwit 1995 challenge was obtained with all heterologous regimens, including the Ad26 and MVA vaccine regimen. All heterologous prime-boost regimens induced comparable immune responses against the EBOV Mayinga GP. Independently of the vaccine regimen, a strong boost effect was seen after heterologous prime-boost immunization. Two additional studies involving more animals have been performed, to strengthen the robustness of the nonclinical efficacy data, and also to optimize the prime-boost schedule so as to obtain induction of protective immunity as quickly as possible, to specifically respond to the Ebola virus disease outbreak in West Africa. Complete survival was observed with 8-week heterologous regimens with Ad26.ZEBOV as prime and MVA-BN-Filo as boost, whereas a high dose of MVA-BN-Filo in these regimens was associated with complete protection against Ebola virus disease. Partial protection was observed with both MVA-BN-Filo as a prime immunization and a shorter prime/boost interval.

Toxicology

A repeated-dose toxicity study in rabbits was performed with prime-boost combinations of Ad26.ZEBOV and MVA-BN-Filo. The different dose regimens were well tolerated when administered twice by intramuscular (IM) injection to New Zealand White rabbits with a 14-day interval period. All vaccine dosing regimens resulted in detectable EBOV GP-specific antibody titers. No significant toxicological effects (no adverse effects) were observed. The immune response was associated with transient increases in fibrinogen, C-reactive protein, globulin, decreases in hematocrit and hemoglobin, and microscopic findings in draining iliac lymph nodes, spleen and at the injection sites. The findings were noted to be recovering over a 14-day treatment-free period and were considered to reflect a physiological response associated with vaccination. There were no effects noted that were considered to be adverse.

In an embryofetal and pre- and postnatal development study in female rabbits, there was no maternal or developmental toxicity following maternal exposure to the vaccine regimens during the premating and gestation period. All vaccine regimens elicited detectable EBOV GP-specific maternal antibody titers that were transferred to the fetuses.

Biodistribution

Single-dose biodistribution studies in rabbits were performed using the MVA-BN vector or the Ad26 vector in combination with another insert (Ad26.ENVA.01: an experimental, prophylactic

Ad26 vector expressing the human immunodeficiency virus [HIV] type 1, Clade A envelope protein). MVA-BN distributed to the skin, muscle, blood, spleen, lung, liver, and pooled lymph nodes and was rapidly cleared (within 48 hours following vaccination). Ad26.ENVA.01 was primarily localized in the injection site muscle, the regional lymph nodes and the spleen. Three months after the single IM injection of Ad26.ENVA.01, the vaccine was cleared from most of the examined tissues. As biodistribution is dependent on the vector platform (MVA or Ad26) and not on the insert, it can be assumed that recombinant MVA-BN-Filo or Ad26.ZEBOV is distributed in the same way as the MVA-BN vector or Ad26.ENVA.01 vector, respectively.

Clinical Studies

To date, the results of the primary analysis of 4 Phase 1 clinical studies with Ad26.ZEBOV and/or MVA-BN-Filo are available (VAC52150EBL1001, VAC52150EBL1002, VAC52150EBL1003, and VAC52150EBL1004). Currently, the clinical program to assess the safety/tolerability and immunogenicity of Ad26.ZEBOV and MVA-BN-Filo consists of 5 Phase 1 (VAC52150EBL1001, VAC52150EBL1002, VAC52150EBL1003, VAC52150EBL1004, and VAC52150EBL1005), 3 Phase 2 (VAC52150EBL2001, VAC52150EBL2002, and VAC52150EBL2003) and 3 Phase 3 clinical studies (VAC52150EBL3001, VAC52150EBL3002, and VAC52150EBL3003), where monovalent Ad26.ZEBOV vaccine and multivalent MVA-BN-Filo vaccine are combined in homologous or heterologous prime-boost regimens in which each vector is used to prime a filovirus-specific immune response followed by a boost immunization with the same or the other vector 2 to 12 weeks later. To date, approximately 2700 healthy adult subjects have been enrolled in the studies mentioned above. Two additional Phase 1 studies investigating MVA-BN-Filo have been performed (EBL01 and CVD-Mali Ebola Vaccine #1000). Refer to the latest versions of the Ad26.ZEBOV and MVA-BN-Filo Investigator's Brochures and Addenda (if applicable) for more details.[5,6]

Limited data from the ongoing Phase 1 studies with Ad26.ZEBOV and MVA-BN-Filo are available.

VAC52150EBL1001, a first-in-human study, is a randomized, placebo-controlled, observer-blind study in healthy adults evaluating the safety, tolerability and immunogenicity of 4 placebo-controlled regimens using MVA-BN-Filo at a dose of $1x10^8$ 50% tissue culture infective dose ($TCID_{50}$) and Ad26.ZEBOV at a dose of $5x10^{10}$ viral particles (vp): 2 regimens with MVA-BN-Filo as prime and Ad26.ZEBOV as boost at a 28- or 56-day interval, and 2 regimens with Ad26.ZEBOV as prime and MVA-BN-Filo as boost at a 28- or 56-day interval. A fifth regimen, with Ad26.ZEBOV at a dose of $5x10^{10}$ vp as prime, and MVA-BN-Filo at a dose of $1x10^8$ $TCID_{50}$ at a 14-day interval was evaluated in an open-label, uncontrolled fashion in healthy adults. VAC52150EBL1001 has enrolled 87 subjects and primary analysis data for safety and immunogenicity are available for 85 subjects (performed when all subjects had completed their 21-day post-boost visit or discontinued earlier).[2] No deaths or adverse events of special interest were reported. Two subjects in the 14-day regimen who experienced grade 3 neutropenia did not receive the boost vaccination as they met criteria for contraindications to boost (specified

in the protocol), but continued scheduled assessments as planned. There were no serious adverse events related to the study vaccines.

In the placebo-controlled regimens, overall frequencies of solicited local and solicited systemic adverse events were higher after MVA-BN-Filo and Ad26.ZEBOV, relative to placebo. In addition, there was a trend towards higher overall frequencies of solicited local and solicited systemic events after Ad26.ZEBOV, relative to MVA-BN-Filo. This trend was not observed in the open-label 14-day regimen. The most frequent solicited local adverse event was injection site pain. The most common solicited systemic adverse events were fatigue, headache and myalgia. Grade 3 solicited local adverse events occurred in 3 subjects (injection site pain and injection site swelling in 1 subject each, injection site erythema in 2 subjects). These events occurred after Ad26.ZEBOV vaccination. Grade 3 solicited systemic events were also reported in 3 subjects (nausea and headache in 2 subjects each, myalgia and fatigue in 1 subject each). All these events occurred after Ad26.ZEBOV, except fatigue which occurred after placebo. The systemic events after Ad26.ZEBOV were considered to be at least possibly related to vaccination by the investigator. In the open-label regimen, no subjects experienced grade 3 solicited local events. Grade 3 solicited systemic events occurred in 3 subjects after Ad26.ZEBOV (chills and fatigue in 3 subjects each, headache in 2 subjects, pyrexia and nausea in 1 subject each). All were considered to be at least possibly related to vaccination by the investigator. No grade 3 solicited systemic events were reported after MVA-BN-Filo. All solicited (local or systemic) adverse events were transient in nature and resolved without sequelae. In the placebo-controlled regimens, the overall frequency of unsolicited adverse events was generally comparable between Ad26.ZEBOV, MVA-BN-Filo, and placebo recipients. In the open-label regimen, unsolicited adverse events were more common after Ad26.ZEBOV than after MVA-BN-Filo.

Overall, the reported adverse events following vaccination were mild in the majority of subjects, transient in nature, and resolving without sequelae. These findings are consistent with the safety profiles observed for similar vaccines. The safety profile of the individual vaccines when used as prime was comparable to that when used as boost.

There was no apparent influence of the prime-boost interval (28 days or 56 days) on the safety profiles of the vaccines. The 14-day prime-boost interval seemed to be associated with higher frequencies of solicited adverse events relative to the 28-day and 56-day prime-boost intervals; however, due to the open-label design of the 14-day regimen, knowledge of the treatment assignment may have biased subjects' reporting.

Both vaccination sequences tested (ie, Ad26.ZEBOV prime followed by MVA-BN-Filo boost and MVA-BN-Filo prime followed by Ad26.ZEBOV boost) were highly immunogenic and induced considerable humoral and cellular immune responses. Extending the interval between the prime and boost led to increased antibody responses (magnitude at a 56-day prime-boost interval was about 1.8 times higher than at a 28-day prime-boost interval), while the effect was less pronounced or the reverse for T cell responses. The induced immune responses were functional, as demonstrated by the neutralizing activity of the antibody responses in all subjects. The composition of induced T cell response was favorable, with a high percentage of

polyfunctional T cells, which generally are thought to play a role in immunological memory and effector functions.

VAC52150EBL1002 is a randomized, placebo-controlled, observer-blind study in healthy adults evaluating the safety, tolerability and immunogenicity of heterologous and homologous prime-boost regimens using MVA-BN-Filo and Ad26.ZEBOV administered in different doses, sequences and schedules: MVA-BN-Filo ($1x10^8$ $TCID_{50}$) as prime followed by a Ad26.ZEBOV ($5x10^{10}$ vp) as boost at 14, 28, or 56 days after prime; Ad26.ZEBOV ($5x10^{10}$ vp) as prime followed by MVA-BN-Filo ($1x10^8$ $TCID_{50}$) as boost at 28 days after prime; Ad26.ZEBOV ($5x10^{10}$ vp) as prime followed by a high dose of MVA-BN-Filo ($4.4x10^8$ $TCID_{50}$) as boost at 14 days after the prime; a high dose of Ad26.ZEBOV ($1x10^{11}$ vp) as prime followed by a high dose of MVA-BN-Filo ($4.4x10^8$ $TCID_{50}$) as boost at 28 days after the prime. All planned 128 subjects of VAC52150EBL1002 have received a prime dose, and 126 subjects have received a boost dose (2 subjects were withdrawn). No vaccine-related serious adverse events have been reported and no safety issues have been identified to date.

VAC52150EBL1003 and VAC52150EBL1004 are randomized, placebo-controlled, observer-blind studies in healthy adults evaluating the safety, tolerability and immunogenicity of 4 regimens using MVA-BN-Filo at a dose of $1x10^8$ $TCID_{50}$ and Ad26.ZEBOV at a dose of $5x10^{10}$ vp: 2 regimens had MVA-BN-Filo as prime and Ad26.ZEBOV as boost at a 28- or 56-day interval, and 2 regimens had Ad26.ZEBOV as prime and MVA-BN-Filo as boost at a 28- or 56-day interval. The blinded phase of studies VAC52150EBL1003 and 1004 are ongoing with enrollment complete in both studies. The blinded safety profile is similar to that reported in VAC52150EBL1001 and 1002 studies with so far, fewer reports of solicited local and systemic adverse events. No vaccine-related serious adverse events have been reported in either study to date.

Safety data generated with the 2 vaccines are provided below however, for the most recent information regarding the safety data of the 2 vaccines, refer to the latest versions of the Investigator's Brochures.[5,6]

Safety Profile of Ad26.ZEBOV

Ad26.ZEBOV is a monovalent, replication-incompetent Ad26-based vaccine. Only limited clinical data are available for Ad26.ZEBOV. However, adenovirus vaccine programs with other gene inserts have revealed no significant safety issues.[5,6]

Safety Profile of MVA-BN

MVA-BN is a further attenuated version of the MVA virus, which in itself is a highly attenuated strain of the poxvirus Chorioallantois Vaccinia Virus Ankara. MVA-BN induces strong cellular activity as well as a humoral (antibody) immune response and has demonstrated an ability to stimulate a response even in individuals with pre-existing immunity against Vaccinia. One of the advantages of MVA-BN is the virus' inability to replicate in a vaccinated individual. The replication cycle is blocked at a very late stage, which ensures that new viruses are not generated and released. This means that the virus cannot spread in the vaccinated person and none of the

serious side effects normally associated with replicating Vaccinia viruses have been seen with MVA-BN.

MVA-BN (MVA-BN®, trade name IMVAMUNE® outside the European Union [EU], invented name IMVANEX® in the EU) has received marketing authorization in the EU for active immunization against smallpox in adults, and in Canada for adults who have a contraindication to the first or second generation smallpox vaccines including people with immune deficiencies and skin disorders.[4] A Phase 3 clinical study has been performed in the US (POX-MVA-013). Results of completed and ongoing clinical studies of MVA-BN-based vaccines in more than 8,100 individuals, including elderly, children and immunocompromised subjects in whom replicating vaccines are contraindicated, have shown that the platform displays high immunogenicity and a favorable safety profile.[7] Across all clinical studies, no trends for unexpected or serious adverse reactions due to the product were detected.

Safety information was combined from the first 2 studies of MVA-BN-Filo (VAC52150EBL1001 and VAC52150EBL1002). In general, MVA-BN-Filo has been shown to be well tolerated.[6]

Three fifths of the subjects reported at least one local site reaction (injection site pain, tenderness, warmth, redness, swelling and/or itching) following administration of MVA-BN-Filo; mostly of mild severity. The most common reported local site reaction was pain at the injection site. All the local reactions resolved to normal without any lasting effects.

At least one general symptom was reported in two fifths of the subjects following MVA-BN-Filo administration. The most common general symptoms were fatigue, headache, myalgia (muscle pain) and nausea. All general symptoms were transient and resolved without lasting effects.

Changes in laboratory tests were reported following MVA-BN-Filo administration which included hypokalemia and decreased numbers of neutrophils (neutropenia). Both changes in laboratory tests were seen in similar numbers of participants following MVA-BN-Filo and the dummy (placebo) vaccine. Less frequently, events of decreased hemoglobin levels were reported. The changes in laboratory tests were not associated with any complaints or symptoms.

Extensive nonclinical studies support the safety profile of the MVA-BN strain.[8,9]

1.2. Benefit/Risk Section

For the most recent information about the benefit/risk assessment of Ad26.ZEBOV and MVA-BN-Filo, refer to the latest versions of the Investigator's Brochures.[5,6]

1.2.1. Known Benefits

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

1.2.2. Potential Benefits

Subjects may benefit from clinical testing and physical examination in the Phase 1, 2 and 3 clinical studies and from continued contact for safety follow-up in the current study; others may benefit from the knowledge that they may aid in the development of an Ebola vaccine.

1.2.3. Known Risks

To date, there are only limited data from the Phase 1 studies with Ad26.ZEBOV and MVA-BN-Filo available. However, Ad26- and Ad35-based vaccines with other gene inserts have been administered to a limited number of human volunteers in clinical studies. These other vaccines mainly elicited some solicited local and systemic reactions, as expected with injectable vaccines, and no serious safety concerns in study participants. MVA-BN-based vaccines have been administered to more than 8,100 individuals without unexpected or serious adverse reactions reported. For details, see the safety data presented in Section 1.1.

1.2.4. Potential Risks

The following potential risks for Ad26.ZEBOV and MVA-BN-Filo will be considered in this study, taking into consideration that this rollover study does not include further administration of the candidate vaccines during the study period:

Vaccine Induced Seropositivity (VISP)

In general, uninfected subjects who participate in Ebola vaccine studies may develop Ebola-specific antibodies as a result of an immune response to the candidate Ebola vaccine, referred to as 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.

Pregnancy and Birth Control

The effect of the study vaccines on a fetus or nursing baby is unknown, as well as the effect on semen. Therefore, a pregnancy with estimated conception within 28 days of vaccination with MVA-BN-Filo or within 3 months of vaccination with Ad26.ZEBOV in a female subject vaccinated with Ad26.ZEBOV and/or MVA-BN-Filo in Phase 1, 2 or 3 clinical studies will be followed up in this study. This study includes no further requirements for birth control as all rollover subjects have completed the vaccination phase.

There may be other serious risks that are not known.

1.2.5. Overall Benefit/Risk Assessment

Since this is an observational safety study, there is no additional risk by participating in this study.

1.3. Overall Rationale for the Study

The safety profile of Ad26.ZEBOV and MVA-BN-Filo needs to be established through evaluation of safety data for periods longer than those that are available from the Phase 1, 2 and 3 clinical studies. Extended follow-up permits the identification of serious adverse events not detected during initial follow-up period in the vaccine clinical study. A long-term observational study will permit the collection of product safety information over an extended period of time, without affecting the requirement for brief clinical studies to support a responsive cycle of clinical development decisions. Additionally, the establishment of a long-term safety study for follow-up of subjects exposed to Ad26.ZEBOV and/or MVA-BN-Filo has been requested by Health Authorities of countries where Phase 1, 2 or 3 clinical studies will be conducted.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

This study will document the long-term safety profile of Ad26.ZEBOV and MVA-BN-Filo in subjects previously exposed to these vaccines in a Phase 1, 2, or 3 clinical study and aims to address gaps in the currently available data for the risks of Ad26.ZEBOV and/or MVA-BN-Filo.

The study objectives are:

- To collect serious adverse event information from subjects exposed to Ad26.ZEBOV and/or MVA-BN-Filo in a Phase 1, 2, or 3 clinical study, for a total of 60 months after prime vaccination (including the duration in the subject's original study).
- To collect pregnancy outcomes (including spontaneous/elective abortion, intrauterine death/stillbirth, information on delivery) and serious adverse event information during pregnancy from female subjects who became pregnant with estimated conception within 28 days after vaccination with MVA-BN-Filo or within 3 months after vaccination with Ad26.ZEBOV in a Phase 1, 2 or 3 clinical study.
- To collect serious adverse event information for up to 60 months after birth from children born to female subjects who became pregnant with estimated conception within 28 days after vaccination with MVA-BN-Filo or within 3 months after vaccination with Ad26.ZEBOV in a Phase 1, 2 or 3 clinical study.

2.2. Hypothesis

This is a descriptive study to document the long-term safety profile of Ad26.ZEBOV and/or MVA-BN-Filo and to address gaps in the currently available data for the risks of Ad26.ZEBOV and/or MVA-BN-Filo. As this study aims to describe the data for benefit-risk assessment purposes, no hypotheses are pre-specified.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a multi-country, prospective, long-term clinical safety study designed to extend the total follow-up period of vaccinated subjects up to 60 months (including the duration in the subject's original study), to allow collection of serious adverse events and pregnancy outcomes (including

spontaneous/elective abortion, intrauterine death/stillbirth, information on delivery) following administration of Ad26.ZEBOV and/or MVA-BN-Filo for the prevention of Ebola virus disease among subjects who participated in a Phase 1, 2 or 3 clinical study. In addition, offspring from vaccinated female subjects who became pregnant with estimated conception within 28 days after vaccination with MVA-BN-Filo or within 3 months after vaccination with Ad26.ZEBOV in a Phase 1, 2 or 3 clinical study will be followed up to 60 months after birth. Up to approximately 3,000 subjects may potentially be enrolled in this study, based on the number of exposed subjects in the contributing Phase 1, 2 or 3 clinical studies.

Since validated assays are not available yet to assess immune responses in the ongoing Phase 2 and 3 studies, unblinding of these studies has been delayed. Therefore, subjects in the ongoing Phase 2 and 3 studies who reach the last study visit will be approached to consent for enrollment into the VAC52150 Vaccine Development Roll-over study for long-term safety surveillance (for a total of up to 60 months after the prime vaccination). After unblinding of their original study only subjects who received Ad26.ZEBOV and/or MVA-BN-Filo will remain in this VAC52150 Vaccine Development Roll-over study for long-term safety surveillance. After unblinding, subjects who received placebo and have already been enrolled into the VAC52150 Vaccine Development Roll-over study will be discontinued from further participation in this roll-over study. This also applies to pregnant subjects who received placebo (ie, subjects enrolled in Cohort 2) or offspring from vaccinated female subjects who received placebo (ie, subjects enrolled in Cohort 3).

The study will consist of an enrollment visit, a number of follow-up contacts and an end-of-study contact. These contacts are preferably conducted by phone; if not possible, a study site visit needs to be organized. Preferably, offspring from vaccinated female subjects will visit the study site for every study visit. If not possible, the child may be visited at home by study site staff or a qualified health care worker for data collection.

Data collection can start when a signed informed consent form (ICF) is available for the current study. Preferably, signing of the ICF occurs at the last visit of the subject's original study (or at birth for offspring). If this is not possible, baseline data will be collected when a signed ICF is available and data need to be captured retrospectively up to the moment of enrollment in the current study.

Data collection will be as follows for the 3 cohorts:

Cohort 1: Data for subjects vaccinated with Ad26.ZEBOV and/or MVA-BN-Filo (or placebo) in a Phase 1, 2 or 3 clinical study (adults, adolescents and children) and who consent to participation in the current study will be collected in 6-month intervals. Data collection will continue for a total of 60 months after prime vaccination (including the duration in the subject's original study).

Cohort 2: Data on the pregnancy outcome of female subjects who became pregnant with estimated conception within 28 days after vaccination with MVA-BN-Filo (or placebo) or within 3 months after vaccination with Ad26.ZEBOV (or placebo) in a Phase 1, 2 or 3 clinical study

and who consent to participation in the current study will be collected at notification of the pregnancy, and at the end of the pregnancy. These subjects will be followed in Cohort 2 up to the end of their pregnancy. Thereafter, female subjects will continue to be followed in Cohort 1 (to reach a total of 60 months follow-up after prime vaccination including the duration in the subject's original study); live-born children will be followed in Cohort 3.

Cohort 3: Data for children born to female subjects exposed to Ad26.ZEBOV and/or MVA-BN-Filo (or placebo) in a Phase 1, 2 or 3 clinical study who became pregnant with estimated conception within 28 days after vaccination with MVA-BN-Filo (or placebo) or within 3 months after vaccination with Ad26.ZEBOV (or placebo) and for whom consent for the current study is given will be collected in 6-month intervals and up to 60 months after birth.

Each local authority will determine which cohorts will be opened for enrollment in their region. It is not mandatory to open all cohorts for enrollment. As a result, a local authority may restrict enrollment to 1 or 2 cohorts, rather than allowing enrollment in all cohorts.

After unblinding of their original study, subjects from Cohort 1 and 2 who received placebo or offspring (Cohort 3) from female subjects who received placebo will be discontinued from further participation in this roll-over study.

The study is considered completed with the last data collection time point for the last subject participating in the study. Further details of study completion and termination procedures are presented in Section 17.9.

Relevant Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and Health Authority approvals will be secured prior to initiating the study.

3.2. Study Design Rationale

The prospective design of the study was chosen to specifically meet the study objectives. Prospective data collection facilitates active pharmacovigilance via real-time identification and reporting of serious adverse events and facilitates collection of a sufficient quantity of defined variables to address the study objectives of characterizing serious adverse events and pregnancy outcomes. The study design was chosen to observe long-term safety outcomes following Phase 1, 2 and 3 clinical studies.

4. TREATMENT ALLOCATION AND BLINDING

This section is not applicable, since no vaccine will be administered in the current study and subjects are already unblinded in their original Phase 1, 2 or 3 clinical study.

Unblinding of the ongoing Phase 2 and 3 studies has been delayed. Therefore, under Amendment 1, subjects who received placebo in their original Phase 2 or 3 study will also be approached for enrollment into the VAC52150 roll-over study before unblinding of their original study.

5. SUBJECT POPULATION

The study will be open to subjects who participated in a Phase 1, 2 and 3 clinical study with Ad26.ZEBOV and/or MVA-BN-Filo and who received at least one dose of study vaccine (active vaccine or placebo). Up to approximately 3,000 subjects may potentially be enrolled in this study, based on the number of exposed subjects in the contributing Phase 1, 2 or 3 clinical studies.

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

For a discussion of the statistical considerations of subject selection, refer to Section 11.2.

5.1. Inclusion Criteria

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

1. Criteria modified per amendment 1

1.1 Criterion modified per amendment 2

1.2 Male or female who participated in a Phase 1, 2 or 3 clinical study with Ad26.ZEBOV and/or MVA-BN-Filo and has been exposed to Ad26.ZEBOV and/or MVA-BN-Filo (or placebo) (Cohort 1);

or

Female who participated in a Phase 1, 2 or 3 clinical study with Ad26.ZEBOV and/or MVA-BN-Filo and became pregnant with estimated conception within 28 days after vaccination with MVA-BN-Filo (or placebo) or within 3 months after vaccination with Ad26.ZEBOV (or placebo) (Cohort 2);

or

Child born to a female subject exposed to Ad26.ZEBOV and/or MVA-BN-Filo (or placebo) in a Phase 1, 2, or 3 clinical study who became pregnant with estimated conception within 28 days after vaccination with MVA-BN-Filo (or placebo) or within 3 months after vaccination with Ad26.ZEBOV (or placebo) (Cohort 3).

Note: Each local authority will determine which cohorts will be opened for enrollment in their region. It is not mandatory to open all cohorts for enrollment. As a result, a local authority may restrict enrollment to 1 or 2 cohorts, rather than allowing enrollment in all cohorts.

2. Must sign an ICF for the current study (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study (or let their child participate).

   Note: Assent is also required of children capable of understanding the nature of the study (typically 7 years of age and older) as described in Section 16.2.3.

5.2. Exclusion Criteria

No exclusions beyond those not meeting the inclusion criteria will be made for participation.

6. DOSAGE AND ADMINISTRATION

This section is not applicable, since no vaccine will be administered in the current study. For details on the administered study vaccine, refer to the protocol of the subject's original study.

7. TREATMENT COMPLIANCE

This section is not applicable, since no study vaccine will be administered in the current study.

8. MEDICATION AND VACCINATIONS

After a signed ICF is obtained for the current study, medications taken for serious adverse events occurring within the entire study follow-up period of 60 months after prime vaccination (ie, limited to medication taken within a period of 30 days prior to the onset of a serious adverse event and up to the resolution of the serious adverse event), or vaccinations administered since exposure to Ad26.ZEBOV and/or MVA-BN-Filo (or placebo) (including routine vaccinations for children) will be documented from baseline (if not already present in the analysis data set from the subject's original study) until the end of data collection.

9. STUDY EVALUATIONS

9.1. Study Procedures

The Time and Events Schedule summarizes the frequency and timing of data collection in this study. The documentation of data must be performed according to Good Clinical Practice (GCP) and professional guidelines.

Prior to data collection, all subjects or their parent/legally acceptable representative (where applicable) must sign an ICF for the current study indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study or let their child participate. Preferably, consent will be obtained at the last visit of the subject's original study or at birth for offspring. If this is not possible, the consent can be given at a later time point, allowing collection of baseline data to be conducted retrospectively up to the moment of enrollment in the current study. Relevant data should be copied from the analysis data set of the subject's original study. Any relevant new information should be added to the CRF of the current study.

Where available (and applicable to the cohort), the following items are to be documented or captured from the original analysis data set at baseline and/or during the long-term follow-up period:

- Demographic data (at baseline only);
- Serious adverse events
- Any medication taken within a period of 30 days prior to the onset of a serious adverse event and up to the resolution of serious adverse event;
- Vaccinations (including routine vaccinations for children);
- Pregnancy follow-up, including information on obstetric history, maternal/paternal risk factors, pregnancy outcome (including spontaneous/elective abortion, intrauterine death/stillbirth, information on delivery);
- Follow-up of offspring, including information on birth (preterm/full term), growth measurements at birth and subsequent visits (height and weight, including growth percentiles), presence of birth defects, medical interventions beyond routine interventions at birth. Medical history of the child may include relevant information from the mother's pregnancy follow-up, family history of growth (details on stature of parents and siblings).

Participating sites will enter data into the CRF into an electronic data collection (eDC) system. The CRF will direct the site regarding which data are required for collection. Participating sites will be trained on the use of the eDC system. Data collected should be recorded accurately, correctly and promptly for each subject during the study. Further details of CRF completion procedures are presented in Section 17.5.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a site visit log that will be kept at the participating site. Further details of monitoring procedures are presented in Section 17.8.

When an enrolled subject completes or withdraws from the study, the investigator will complete an end-of-study form for the individual subject and provide a specific date for the end-of-study observation(s). When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source documents (see Section 10 for details).

After unblinding of their original study, subjects who received placebo will be withdrawn from further participation. This also applies to pregnant subjects who received placebo (ie, subjects enrolled in Cohort 2) or offspring from vaccinated female subjects who received placebo (ie, subjects enrolled in Cohort 3).

Subjects who appear to be lost to follow-up will be contacted, per local practice, and the data recorded in the CRF. Subjects unable to be reached within 365 days of their last follow-up will be considered "lost to follow-up" unless subsequent contact is established. Subjects lost to follow-up will have all data included for analysis unless the subject had specified upfront that their data is to be excluded from analysis.

9.2. Safety

9.2.1. Exposure Definition

Exposure to Ad26.ZEBOV and/or MVA-BN-Filo vaccines (or placebo) will be determined by documentation from the Phase 1, 2 and 3 clinical studies. The exposure date to any component of Ad26.ZEBOV and/or MVA-BN-Filo (or placebo) for each subject will be the vaccine administration date as obtained from the CRF from the subject's original study.

9.2.2. Evaluations

Serious Adverse Events

For the prospective study period, all serious adverse events, related or not related, following exposure of subjects to Ad26.ZEBOV and/or MVA-BN-Filo (or placebo) or in offspring are to be recorded in the CRF and in the subject's source documents.

Section 12 provides further details of safety reporting procedures.

Any serious adverse events 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.

Pregnancy Outcomes

For the prospective study period, all pregnancy outcomes (including spontaneous/elective abortion, intrauterine death/stillbirth, information on delivery) following pregnancy of a female subject who became pregnant with estimated conception within 28 days after vaccination with MVA-BN-Filo (or placebo) or within 3 months after vaccination with Ad26.ZEBOV (or placebo) are to be recorded in the CRF and in the subject's source documents.

Growth Measurements

For the prospective study period, growth measurements for offspring (including height, weight and growth percentiles) are to be recorded in the CRF and in the subject's source documents.

9.2.3. Endpoints

Refer to Section 11.1 for the endpoints.

10. SUBJECT COMPLETION/WITHDRAWAL FROM THE STUDY

When an enrolled subject completes or withdraws from the study, the investigator will complete an end-of-study form for the individual subject and provide a specific date for the end-of-study observation(s).

10.1. Completion

Cohort 1: Data for subjects vaccinated with Ad26.ZEBOV and/or MVA-BN-Filo (or placebo) in a Phase 1, 2 or 3 clinical study (adults, adolescents and children) and who consent to participation in the current study will be collected in 6-month intervals. Data collection will

continue for a total of 60 months after prime vaccination (including the duration in the subject's original study).

Cohort 2: Data on the pregnancy outcome of female subjects who became pregnant with estimated conception within 28 days after vaccination with MVA-BN-Filo (or placebo) or within 3 months after vaccination with Ad26.ZEBOV (or placebo) in a Phase 1, 2 or 3 clinical study and who consent to participation in the current study will be collected at notification of the pregnancy, and at the end of the pregnancy. These subjects will be followed in Cohort 2 up to the end of their pregnancy. Thereafter, female subjects will continue to be followed in Cohort 1 (to reach a total of 60 months follow-up after prime vaccination including the duration in the subject's original study); live-born children will be followed in Cohort 3.

Cohort 3: Data for children born to female subjects exposed to Ad26.ZEBOV and/or MVA-BN-Filo (or placebo) in a Phase 1, 2 or 3 clinical study who became pregnant with estimated conception within 28 days after vaccination with MVA-BN-Filo (or placebo) or within 3 months after vaccination with Ad26.ZEBOV (or placebo) and for whom consent for the current study is given will be collected in 6-month intervals, and up to 60 months after birth.

Refer to Section 10.2 for details on the withdrawal of subjects after unblinding of their original study.

10.2. Withdrawal From the Study

A subject may be withdrawn from data collection in this study for any of the following reasons:

- Withdrawal of consent
- Lost to follow-up
- Death

After unblinding of their original study, subjects who received placebo will be withdrawn from further participation. This also applies to pregnant subjects who received placebo (ie, subjects enrolled in Cohort 2) or offspring from vaccinated female subjects who received placebo (ie, subjects enrolled in Cohort 3).

Subjects who are subsequently enrolled as a subject in another non-sponsor clinical study do not need to be withdrawn from the study. It is accepted that data collection in this study may be restricted by confidentiality agreement terms and/or conditions of another concurrent clinical study.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source documents.

If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for withdrawal. The measures taken to follow up must be documented. In the event that the status of the subject cannot be determined and the

subject is considered to be lost to follow-up, an end-of-study form for the individual subject will be completed and a specific date for the last observation will be provided.

11. STATISTICAL METHODS

Statistical analysis will be performed by or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the data collected in this study is outlined below. Specific details will be provided in the Statistical Analysis Plan.

11.1. Endpoints

The following endpoints will be analyzed:

- Incidence of serious adverse events in subjects exposed to Ad26.ZEBOV and/or MVA-BN-Filo in a Phase 1, 2 or 3 clinical study, up to 60 months after prime vaccination.
- Incidence of pregnancy with estimated conception within 28 days after vaccination with MVA-BN-Filo or within 3 months after vaccination with Ad26.ZEBOV.
- Incidence of pregnancy by pregnancy outcome.
- Incidence of live-born children from a pregnancy with estimated conception within 28 days after vaccination with MVA-BN-Filo or within 3 months after vaccination with Ad26.ZEBOV.
- Incidence of serious adverse events in children born from a pregnancy with estimated conception within 28 days after vaccination with MVA-BN-Filo or within 3 months after vaccination with Ad26.ZEBOV up to 60 months after birth.

11.2. Sample Size Determination

The enrollment projections of the contributing Phase 1, 2 and 3 clinical studies are estimated to result in enrollment of up to approximately 3,000 subjects.

The proposed study is based on analysis of prospective cohort data provided by investigators on subjects exposed to Ad26.ZEBOV and/or MVA-BN-Filo (or placebo). The study may include bias related to the observational nature of the data and potential lack of data due to loss to follow-up or essential data not collected routinely. Loss to follow-up may be pronounced in countries where infrastructure for data collection is lacking. Additionally, the study's ability to detect serious adverse events and the precision of these rates are based on the number of subjects participating in the study and completing study follow-up; however, this number is unknown.

11.3. Analysis Sets

The Full Analysis set includes all subjects who were enrolled in this study and have at least one post-baseline visit, regardless of the occurrence of protocol violations.

The Restricted Analysis set includes all subjects who were enrolled in this study and have at least one post-baseline visit, have no major protocol deviations deemed to affect safety endpoints and have not been enrolled in any other clinical study.

The study endpoints will be analyzed based on the Full Analysis set as the primary analysis population. Additionally, the study endpoints may be analyzed based on the Restricted Analysis set as a secondary analysis population (sensitivity analysis).

11.4. Subject Information

Baseline characteristics as recorded in the subject's original study, including demographics, medical and vaccination history will be summarized by cohort and original randomization (active vaccine versus placebo). Categorical variables will be summarized by frequency distribution (number and percentage of subjects) and continuous variables will be summarized by descriptive statistics (including mean, median, standard deviation).

11.5. Safety Analyses

The verbatim terms used in the CRF by investigators to document serious adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All serious adverse events will be included in the analysis. For each serious adverse event, the percentage of subjects who experience at least 1 occurrence of the given event and the number of events per person-year (where applicable) with corresponding 2-sided 95% confidence intervals will be provided, for each cohort and by original randomization (active vaccine versus placebo). In addition, these analyses will be provided by age group for Cohort 1.

The incidence of pregnancy, incidence of pregnancy outcomes (including spontaneous/elective abortion, intrauterine death/stillbirth, information on delivery) and incidence of live-born children will be summarized by original randomization (active vaccine versus placebo). Only pregnancies with estimated conception within 28 days after vaccination with MVA-BN-Filo or within 3 months after vaccination with Ad26.ZEBOV, and live-born children from these pregnancies, will be included.

Results for subjects who received active vaccine or placebo will be presented separately.

A summary for subjects who die or who discontinue due to a serious adverse event will be provided.

The use of medications taken in relation to serious adverse events will be summarized.

Additional summaries, listings, datasets, or subject narratives may be provided, as appropriate.

11.6. Statistical Analysis

No formal statistical testing of safety data is planned.

11.7. Interim Analyses

There are no planned interim analyses. However, the accumulating data during study conduct may be used for reporting required for health authority submissions or other purposes. As this is a non-comparative study without formal hypotheses, any interim data may be used for purely administrative purposes without having an impact on study conduct or need for statistical

adjustments. All interim reporting must be approved by the study responsible physician and project statistician prior to conduct.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, 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.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

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

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

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study vaccine and the event, the event must be reported as a serious and unexpected suspected adverse reaction (SUSAR) even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For Ad6.ZEBOV and MVA-BN-Filo, the

expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure and Addenda, if applicable. [5,6]

Adverse Event With a Causal Relationship to a Study Vaccine

An adverse event is considered to have a causal relationship to a study vaccine if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

An adverse event is considered to have no causal relationship to the study vaccine if the attribution is not related or doubtful by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Every effort should be made by the investigator to explain any adverse event and to assess its potential causal relationship, ie, to administration of the study vaccine or to alternative causes, eg, natural history of underlying disease(s), concomitant drug(s). This applies to all adverse events, whether serious or non-serious. Assessment of causality must be done by a licensed study physician (the investigator or designee).

The investigator will use the following guidelines to assess the causal relationship of an adverse event to study vaccine:

Not Related

An adverse event that is not related to the use of the study vaccine.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the study vaccine. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the study vaccine. The relationship in time is suggestive. An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive.

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

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

- Adverse events of special interest known for Ad26.ZEBOV and MVA-BN-Filo[5,6]

These safety events may not meet the definition of an adverse event; however, from a policy perspective, they are treated in the same manner as adverse events. Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to the local sponsor within 24 hours of them becoming aware of the event.

12.3. Procedures

12.3.1. Serious Adverse Events

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

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

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

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available

- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

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

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

The cause of death of a subject in a study, whether or not the event is expected or associated with the study vaccine, is considered a serious adverse event.

12.3.2. Pregnancy

All initial reports of pregnancy in the Phase 1, 2 or 3 trials with estimated conception within 28 days after vaccination with MVA-BN-Filo (or placebo) or within 3 months after vaccination with Ad26.ZEBOV (or placebo) in female subjects must have been reported to the sponsor by the study-site personnel as described in the respective protocols. Data collection for the pregnancy outcomes (including spontaneous/elective abortion, intrauterine death/stillbirth, information on delivery) will be performed in this study, as well as collection of serious adverse events occurring in the offspring from these subjects.

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

This section is not applicable, since no study vaccine will be administered in this study.

14. STUDY VACCINE INFORMATION

This section is not applicable, since no study vaccine will be administered in this study.

For details on the administered study vaccine in the subject’s original Phase 1, 2 or 3 study, refer to the respective protocol.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure's and Addenda, if applicable
- eDC Manual/electronic CRF Completion Guidelines
- Sample ICF

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects 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 subjects who are fully able to understand the risks and benefits, and who provide their consent voluntarily will be enrolled.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or a legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to subjects who have provided consent (and assent as applicable) refers to the subjects and his or her parent(s) or the subject's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents still want them to participate.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Independent Ethics Committee or Institutional Review Board

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

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

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

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

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

- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

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

16.2.3. Informed Consent and Assent Form

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

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive.

Subjects will be informed of the observational nature of the study, that the sponsor only intends to collect information and that their participation in the study does not involve invasive procedures. Only subjects who are fully able to understand the nature of the study and provide their consent voluntarily will be enrolled.

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

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

Children (minors) or subjects who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. Written assent should be obtained from subjects who are able to write. A separate assent form written in language the subject can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the subject, and to the subject's parent or legally acceptable representative, if applicable. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents still want them to participate.

For children participating in the study when referring to the signing of the participation agreement/ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his/her parent(s) (preferably both parents, if available) or a legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before any data collection.

Personal data collected from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study, and must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations (see Section 16.2.4).

16.2.4. Privacy of Personal Data

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

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

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data 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 subject has the right to request through the investigator access to his or her 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.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

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

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.

- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

17.3. Subject Identification, Enrollment, and Screening Logs

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

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

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

17.4. 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 study contacts; record of all serious adverse events and follow-up of serious adverse events; record and follow-up of pregnancy; medication taken within a period of 30 days prior to the onset of a serious adverse event and up to the resolution of the serious adverse event, and date of study completion and reason for 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).

For children in Cohort 3, the following data will be recorded directly into the CRF and will be considered source data:

- Race
- Height, weight and growth percentiles at birth

For other cohorts, data will be copied from the analysis data set of the subject's original study.

17.5. Case Report Form Completion

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

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the CRF.

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

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

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

17.6. 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 on-site monitoring visits and after their return/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.

The investigator/institution will maintain all CRFs and source documentation that support the data collected for each subject, as well as all study documents specified by the applicable regulatory requirement(s) (see Section 17.2). The investigator/institution will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained for at least 5 years or other appropriate period as defined by local regulations after the completion of the final study report, but will be retained for a longer period if required by applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Further details of record retention policies are provided in Section 17.7.

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 company policy. Similar procedures may also be conducted by a regulatory body. Further details of on-site audit policies are presented in Section 17.10.

17.7. Record Retention

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

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

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

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

17.8. Monitoring

The sponsor will perform on-site monitoring visits. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records, documentation of telephone calls with the subject). 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.

17.9. Study Completion/End of Study

17.9.1. Study Completion

The study is considered completed with the last data collection time point for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final data collection time point at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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

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

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

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

The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

17.10. 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.

17.11. Use of Information and Publication

All information, including but not limited to information regarding Ad6.ZEBOV and MVA-BN-Filo (VAC52150) or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of Ad6.ZEBOV and MVA-BN-Filo (VAC52150), and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data from all study sites that participated in the study.

Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

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.

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1. Clinical Study Report MAL-V-A001. A Phase I/IIa, double-blind, randomized, placebo-controlled, dose-escalation clinical study evaluating safety, tolerability and immunogenicity of two dose levels of recombinant adenoviral serotype Ad35 and serotype Ad26 vectors expressing the malaria *Plasmodium falciparum* circumsporozoite antigen administered as heterologous prime-boost regimen, and assessing protective efficacy of the higher dose in a malaria challenge model in unblinded conditions. Crucell Holland B.V. (Aug 2014).
2. Clinical Study Report VAC52150EBL1001 (Primary Analysis). A Phase 1, first-in-human study to evaluate the safety, tolerability and immunogenicity of heterologous prime-boost regimens using MVA-BN-Filo and A26.ZEBOV administered in different sequences and schedules in healthy adults. Crucell Holland B.V. (Oct 2015).
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5. Investigator's Brochure: JNJ-61210474 (Ad26.ZEBOV), Edition 3. Crucell Holland B.V. (Oct 2015). For updated information, refer to Edition 4 (Janssen Vaccines & Prevention, 23 June 2016).
6. Investigator's Brochure: MVA-BN-Filo (MVA-mBN226B), Edition 6. Bavarian Nordic A/S (Nov 2015). For updated information, refer to Edition 10 (11 July 2016).
7. MVA-BN® (Modified Vaccinia Ankara - Bavarian Nordic). Available at: http://id.bavarian-nordic.com/pipeline/technology-platform/mva-bn.aspx Accessed 19 November 2015.
8. Stittelaar KJ, Kuiken T, de Swart RL et al. Safety of Modified Vaccinia Virus Ankara (MVA) in immune-suppressed macaques. Vaccine. 2001;19(27):3700-3709.
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10. WHO Fact Sheet N°103 Ebola Virus Disease 2014. Available at: http://www.who.int/mediacentre/factsheets/fs103/en/. Accessed 19 November 2015.

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Vaccines & Prevention B.V.

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

(Day Month Year)

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

LAST PAGE

SIGNATURES

Signed by	Date	Justification
PPD	02Mar2017, 14:02:27 PM, UTC	Document Approval