Janssen Vaccines & Prevention B.V. *

Clinical Protocol

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Immunogenicity, Safety, Reactogenicity, and Consistency of a Heterologous 2-dose Vaccine Regimen Using 3 Consecutive Lots of Ad26.ZEBOV and MVA-BN®-Filo in Adult Participants.

Protocol VAC52150EBL3004; Phase 3
AMENDMENT 3

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

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

US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

Status: Approved
Date: 15 June 2020
Prepared by: Janssen Vaccines & Prevention B.V.
EDMS number: EDMS-ERI-175180243, 10.0

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

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PROTOCOL AMENDMENTS

Protocol Version	Date
Original Protocol	19 September 2019
Amendment 1	25 November 2019
Amendment 2	2 April 2020
Amendment 3	This document

Amendments below are listed beginning with the most recent amendment.

Amendment 3 (This document)
The overall reason for the amendment: This amendment responds to the impact of Coronavirus Disease 2019 (COVID-19) on the ability of participants to return within window (±3 days) for Dose 2 in this lot-to-lot consistency study and proposes to widen the window, while maintaining the ability to achieve the primary and secondary objectives of the study.

Applicable Section(s)	Description of Change(s)
Rationale: Shortly after Dose 1 (Ad26.ZEBOV) was administered to the participants, 'stay-at-home' orders were imposed in the cities where the clinical sites are located. Although the sites were able to remain open with appropriate safety measures, a significant number of participants did not return within window for Dose 2 (MVA-BN-Filo) vaccination. The failure-to-return rate was approximately 22% which would likely lead to underpowering for the primary objective. Protocol amendment 2 allows for replacement of subjects in the immunogenicity subset if the dropout rate exceeded 5% due to COVID-19 but did not widen the acceptable time frame to receive Dose 2 and still be able to contribute to the per protocol analysis. Analysis of the variability data of the ELISA assay remains stable when the interval between the 2 vaccines is widened from Day 56 out to Day 85 (data from studies VAC52150EBL2001 and VAC52150EBL2002) and even remains stable when the interval is ≥56 (data from the immunogenicity analysis set from study VAC52150EBL2002). It is noted that while the variability around the ELISA values remains stable, the GMCs increase modestly as the interval of time between doses increases. Because the assignment of the additional participants to the groups will be blinded and random, there should be no impact on our ability to demonstrate comparability between the groups. Given that the variability around the measurement remains stable, assignment to the groups will be random and in the absence of any safety concerns, this amendment will widen the acceptable time frame around Dose 2 to minimize the number of exclusions from the per protocol analysis and will apply to participants already vaccinated in the study. Protocol amendment 2 provided for the recruitment of 2 additional Groups (5 and 6) who will receive a booster dose. These participants have not yet been recruited. It is expected that these additional groups will likely receive their second dose in the fall of 2020, at which time it is possible that a second wave of COVID-19 may occur. The window for Dose 2 for these groups, therefore, is only being increased to 1 week to try to assure that Dose 2 is completed before a recurrence of COVID-19. Furthermore, the window for Dose 2 for Groups 5 and 6 is limited to 1 week since this extension for the window is deemed suitable for the correct interpretation of the anamnestic response to the booster dose. If the window for Dose 2 is further extended such that the time between Dose 2 and the booster dose is decreased, the primary response to the initial 2-dose regimen may not have reached a plateau at the time the booster dose is given and the immune system may be differently susceptible to the booster.	
SYNOPSIS TIME AND EVENTS SCHEDULE ABBREVIATIONS 3.1 Overview of Study Design 11.2 Sample Size Determination 11.3 Immunogenicity Analyses	Clarified the change in visit window around Dose 2 for all groups. Increasing the window around Dose 2 for Groups 1-4. Increasing the window around Dose 2 for Groups 5 and 6. Provided rationale supporting the increase in visit window around Dose 2 while preserving the ability to achieve the primary and secondary objectives. As a sensitivity analyses, both the primary and secondary hypotheses of equivalence will also be tested based on data of participants who received the second vaccination within the original window (±3 days) around the Day 57 visit.

Applicable Section(s)	Description of Change(s)
Rationale: In line with the current protocol template, the Confidentiality Statement on the title page was updated and a footer was added.	
Throughout the document.	

Amendment 2 (2 April 2020)
The overall reason for the amendment: This amendment is written to accommodate a request from EMA to obtain safety and immunogenicity data of a booster dose of Ad26.ZEBOV given 4 months after the primary vaccine regimen.

Applicable Section(s)	Description of Change(s)
Rationale: Administration of a booster dose of Ad26.ZEBOV given at 1- and 2 years post Dose 1 in studies VAC52150EBL1002, VAC52150EBL2002 and VAC52150EBL3001 induced a rapid and robust anamnestic response to the booster vaccine. Administration of a booster dose in anticipation of imminent exposure to Ebola (ie, prior to deployment to an Ebola outbreak area) may be desired as a precautionary measure to optimize protection. However, there are currently no clinical data available on the immunogenicity and safety of such an Ad26.ZEBOV booster dose when administered less than 1 year after the primary vaccine regimen. Booster doses as early as 2-3 months after Dose 2 were assessed in a multivalent filovirus and an HIV vaccine program and were able to induce a marked increase in antibody concentrations, although to a lower magnitude than a later booster. Furthermore, based on the kinetics of decrease in antibody concentrations after the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen, supported by a mechanistic model of antibody persistence and general vaccine knowledge, an Ad26.ZEBOV booster dose administered from 4 months after completion of the primary vaccine regimen is likely to induce a strong anamnestic response based on mature immune memory and to maximize the likelihood of protection in case of imminent risk of exposure to Ebola. Therefore, a separate Booster Cohort of participants will receive the primary vaccine regimen followed by a booster dose of Ad26.ZEBOV 4 months after Dose 2. The participants in this Booster Cohort will be assessed for safety and immunogenicity.	
SYNOPSIS TIME AND EVENTS SCHEDULE 1.2.4 Potential Risks 1.2.5 Overall Benefit/Risk Assessment 1.3 Overall Rationale for the Study 2.1 Objectives and Endpoints 3.1 Overview of Study Design 3.2 Study Design Rationale 4.1 Inclusion Criteria 4.2 Exclusion Criteria 4.3 Prohibitions and Restrictions 5 STUDY VACCINE ALLOCATION AND BLINDING 6 DOSAGE AND ADMINISTRATION 6.1 Criteria for Postponement of Vaccination 6.2 Contraindications to Second Vaccination 8 PRESTUDY AND CONCOMITANT THERAPY 9.1.1 Overview 9.1.2 Screening, Vaccination, Postvaccination Visits, and Follow-up 9.2 Immunogenicity Evaluations 9.3.1 Safety Assessments 10.1 Completion 10.2 Discontinuation of Study Vaccine/Withdrawal From the Study 11 STATISTICAL METHODS 11.1 Analysis Sets 11.2 Sample Size Determination 11.4 Safety Analysis 12.3.1 All Adverse Events 17.4 Source Documentation	An additional cohort of 60 participants will be enrolled in a 5:1 active:placebo ratio. The participants will be given the 2-dose heterologous vaccine regimen, Ad26.ZEBOV followed by MVA-BN-Filo 56 days later, and a booster dose of Ad26.ZEBOV 4 months after Dose 2, or placebo. To all sections listed in the 1st column, details for the Booster Cohort were added.

Applicable Section(s)	Description of Change(s)
Rationale: Due to the recent (on 11 March 2020) WHO-declared COVID-19 pandemic, the following issues may occur: • A potential higher dropout rate (ie, higher than 5%) may occur and/or some participants in the immunogenicity subset may be excluded from primary immunogenicity equivalence testing (Dose 2 not received or received out of window, no attendance or out of window attendance of the 21-day post Dose 2 visit). To mitigate these issues, additional participants may be recruited in the immunogenicity subset. • It may become difficult to conduct study visits on site. Therefore, alternative arrangements to conduct study visits according to the protocol may be considered.	
SYNOPSIS 3.1 Overview of Study Design 11.2 Sample Size Determination	Addition of language regarding extra recruitment in the immunogenicity subset due to issues caused by the COVID-19 pandemic.
TIME AND EVENTS SCHEDULE	Addition of a sentence allowing for alternative arrangements to conduct study visits according to the protocol.
Rationale: In some study participants, missing data were noted due to difficulties in obtaining a blood sample. To avoid this in the future, participants for which it is difficult to obtain blood draws, will be excluded from the study.	
4.2 Exclusion Criteria	Addition of an exclusion criterion specifying that participants for which it is difficult to take a blood sample will not be allowed to enter the study.
Rationale: Minor changes were made throughout the document.	
DEFINITIONS OF TERMS	Addition of the definition of immunogenicity subset for clarity.
1.3 Overall Rationale for the Study	Addition of generic terminology with regards to approval of the vaccine regimen by a regulatory authority.
11.1 Analysis Sets	Replacement of the term protocol violations by protocol deviations.
Attachment 1	Correction of the originating DMID toxicity table version (2014 to 2007).
TIME AND EVENTS SCHEDULE	Minor editorial changes.

Amendment 1 (25 November 2019)

The overall reason for the amendment: This amendment is written in response to the questions received from FDA on 8 November 2019.

Applicable Section(s)	Description of Change(s)
Rationale: The protocol was updated to exclude breast-feeding women as the study is not designed to assess the safety of the vaccine regimen in lactating women.	
4.2 Exclusion Criteria	Exclusion of breast-feeding women as the study is not designed to assess the safety of the vaccine regimen in lactating women.
Rationale: The protocol was updated to add a telephone call between the study participant and the study site personnel for safety purposes at Day 29 (28 days post Dose 1) to promote recall of unsolicited adverse events experienced by study participants. Furthermore, procedures for safety evaluation were further clarified in the protocol.	
SYNOPSIS, TIME AND EVENTS SCHEDULE, 3.1 Overview of Study Design, 9.1.2 Screening, Vaccination, Postvaccination Visits, and Follow-up	Addition of a telephone call between the study participant and the study site personnel for safety purposes at Day 29 (28 days post Dose 1) to promote recall of unsolicited adverse events experienced by study participants.
9.3 Safety Evaluations	Clarification was added on the procedures used for safety evaluation.
SYNOPSIS, 1.2.5 Overall Benefit/Risk Assessment, 3.1 Overview of Study Design, 9.3 Safety Evaluations	Study vaccination pausing rules were added.
Rationale: The protocol was updated to exclude participants with any clinically significant acute or chronic medical condition that in the opinion of the investigator would preclude participation.	
4.2 Exclusion Criteria	Exclusion of participants with any clinically significant acute or chronic medical condition that in the opinion of the investigator would preclude participation.

Applicable Section(s)	Description of Change(s)
Rationale: It was clarified in the protocol that all sponsor personnel involved in the determination of the causality for serious adverse events reported during the study are to remain blinded to vaccine allocation. Furthermore, clarification was added in the protocol for maintaining the study blind and ensuring that non-sponsor study site personnel will not be inadvertently exposed to unblinded data.	
SYNOPSIS, 3.1 Overview of Study Design, 5 STUDY VACCINE ALLOCATION AND BLINDING, 11 STATISTICAL METHODS	Clarification was added that all sponsor personnel involved in the determination of the causality for serious adverse events reported during the study are to remain blinded to vaccine allocation until final database lock.
5 STUDY VACCINE ALLOCATION AND BLINDING	Clarification was added for maintaining the study blind and ensuring that non-sponsor study site personnel will not be inadvertently exposed to unblinded data.
Rationale: Minor errors were noted.	
SYNOPSIS, 3.1 Overview of Study Design, 4.2 Exclusion Criteria	MVA-BN-Filo is contraindicated in individuals with hypersensitivity to the active substance in MVA-BN-Filo or to any of its excipients, or trace residues (chicken or egg protein and gentamicin). The protocol has been updated accordingly.
Throughout the protocol	Minor changes in abbreviation use were made.

SYNOPSIS

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Immunogenicity, Safety, Reactogenicity, and Consistency of a Heterologous 2-dose Vaccine Regimen Using 3 Consecutive Lots of Ad26.ZEBOV and MVA-BN®-Filo in Adult Participants.

Janssen Vaccines & Prevention B.V. (hereafter referred to as the sponsor), in collaboration with Bavarian Nordic GmbH (BN) is developing a prophylactic Ebola vaccine regimen (VAC52150) comprised of the following 2 candidate Ebola vaccines:

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

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

OBJECTIVES, ENDPOINTS, AND HYPOTHESES

Objectives	Endpoints
Primary	
• To demonstrate that the paired 2-dose vaccine regimens from 3 consecutively manufactured lots of Ad26.ZEBOV as Dose 1 and 3 consecutively manufactured lots of MVN-BN-Filo as Dose 2, administered at a 56-day interval, induce an equivalent humoral immune response.	• Binding antibody levels against the EBOV GP using enzyme-linked immunosorbent assay (ELISA, ELISA units/mL [EU/mL]) at 21 days post Dose 2 vaccination.
Secondary	
• To demonstrate that 3 consecutively manufactured lots of Ad26.ZEBOV as Dose 1 induce an equivalent humoral immune response.	• Binding antibody levels against the EBOV GP using ELISA (EU/mL) at 56 days post Dose 1 vaccination.
• To assess the safety and reactogenicity of a heterologous 2-dose vaccine regimen of Ad26.ZEBOV and MVA-BN-Filo administered intramuscularly (IM) on Days 1 and 57, respectively, using 3 different lots of Ad26.ZEBOV and 3 different lots of MVA-BN-Filo.	• Solicited local and systemic adverse events until 7 days post each vaccination. • Unsolicited adverse events until 28 days post each vaccination. • Serious adverse events until the end of the study.
Exploratory (Booster Cohort only)	
• To assess the humoral immune response to a booster dose of Ad26.ZEBOV given 4 months after Dose 2	• Binding antibody levels against the EBOV GP using ELISA (EU/mL) at pre booster (Day 177) and several post booster timepoints (7-days, 21-days, 6-months and 12-months post booster dose)

Objectives	Endpoints
• To assess the safety and reactogenicity of a booster dose of Ad26.ZEBOV	• Solicited local and systemic adverse events until 7 days post booster vaccination. • Unsolicited adverse events until 28 days post booster vaccination. • Serious adverse events until the end of the study.
• To assess the presence of neutralizing antibodies against the Ad26 vector	• Viral neutralizing antibody levels against the Ad26 vector at baseline, pre booster vaccination (Day 177), and at 21 days post booster vaccination.

Hypotheses

The primary hypotheses are:

Null hypothesis:

Three consecutive lots of Ad26.ZEBOV (Lots A, B, and C) as Dose 1 paired sequentially in 3 groups with 3 consecutive lots of MVA-BN-Filo (Lots 1, 2, and 3) as Dose 2 do not induce equivalent geometric mean concentrations (GMCs) of the EBOV GP-specific antibody response 21 days post Dose 2, for at least one pairwise comparison.

Alternative hypothesis:

Three consecutive lots of Ad26.ZEBOV (Lots A, B, and C) as Dose 1 paired sequentially in 3 groups with 3 consecutive lots of MVA-BN-Filo (Lots 1, 2, and 3) as Dose 2 induce equivalent GMCs of the EBOV GP-specific antibody response 21 days post Dose 2, for all 3 pairwise comparisons (ie, Groups 1 versus [vs] 2, 1 vs 3 and 2 vs 3).

Equivalence of any 2 groups (Ad26.ZEBOV as Dose 1 followed by MVA-BN-Filo as Dose 2) will be shown if the 95% confidence interval [CI] of the estimated GMC ratio lies entirely within 0.5 and 2.0. These equivalence limits were chosen primarily based on the population variability as measured by the ELISA assay. Immunogenic equivalence of the 3 different lots of Ad26.ZEBOV (Lots A, B, and C) paired sequentially in 3 groups with 3 different lots of MVA-BN-Filo (Lots 1, 2, and 3) is established if equivalence is shown for all 3 pairwise comparisons.

The secondary hypotheses will be tested on the EBOV GP-specific antibody response 56 days post Dose 1. Similar null and alternative hypotheses will be formulated and tested using the same criteria outlined for the primary hypotheses.

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase 3 study to evaluate lot-to-lot consistency of the manufacturing process by assessing the immunogenicity of the final product of 3 consecutively manufactured lots of Ad26.ZEBOV at a nominal dose of $5x10^{10}$ viral particles (vp) as Dose 1 and 3 consecutively manufactured lots of MVA-BN-Filo at a nominal dose of $1x10^{8}$ infectious units (Inf U) as Dose 2 at a 56-day interval in adult participants (Groups 1-4). Once randomization of this part of the study is finished, an additional Booster Cohort of 60 participants will be enrolled in a 5:1 active:placebo ratio. These participants will be given the 2-dose heterologous vaccine regimen Ad26.ZEBOV followed by MVA-BN-Filo 56 days later, and a booster dose of Ad26.ZEBOV 4 months after Dose 2, or placebo (Groups 5-6).

The 3 consecutive Ad26.ZEBOV drug product lots that will be used in the study have been manufactured at the final manufacturing site (ie, IDT Biologika GmbH in Dessau-Rosslau, Germany [IDT]) and are representative of the final manufacturing process and scale (Lots A, B, and C). The 3 consecutive MVA-BN-Filo drug product lots that will be used have been manufactured at the final manufacturing site (IDT) and are representative of the final manufacturing process and scale (Lots 1, 2, and 3). Lots A, B, and C and Lots 1, 2, and 3 are paired sequentially in 3 groups (ie, A:1 [Group 1], B:2 [Group 2], and C:3 [group 3]). Group 4 will receive 2 placebo vaccinations.

In the main part of the study (Groups 1-4), a planned total number of at least 741 participants will be enrolled. All participants in this part of the study will be assessed for safety and reactogenicity; 456 participants (144 in each of Groups 1 to 3 and 24 in Group 4) will also be assessed for immunogenicity (immunogenicity subset). Participants will be randomly assigned to one of 4 groups in a 6:6:6:1 ratio, ie, to one of the 3 groups receiving Ad26.ZEBOV and MVA-BN-Filo (Groups 1 to 3) with a total of at least 234 participants per group, or to a placebo group (Group 4) with 39 participants, and the first 456 participants belonging to the immunogenicity subset.

Due to the recent (on 11 March 2020) WHO declared COVID-19 pandemic, a potential higher dropout rate (ie, higher than 5%) may occur. In addition, some participants in the immunogenicity subset may be excluded from primary immunogenicity equivalence testing because of:

- Participant not receiving Dose 2; *OR*
- Participant receiving Dose 2 outside the protocol defined window; *OR*
- Participant not attending the 21-day post Dose 2 visit; *OR*
- Participant attending the 21-day post Dose 2 visit outside the protocol-defined window.

To mitigate these issues, additional participants may be recruited in the immunogenicity subset.

Shortly after participants received Dose 1 vaccination, ‘stay-at-home’ orders were imposed in the areas where the sites were located. Although the sites had implemented appropriate safety measures to prevent spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), approximately 22% of participants did not return to the site within the protocol defined windows (±3 days) for Dose 2 administration. Investigators were instructed to bring participants back to the site to complete the vaccine regimen, even if they were out of window. Currently, the stay-at-home orders have been lifted and participants are now able to return to the sites for follow-up. In order to reduce the number of additional participants needed for the primary and secondary immunogenicity analyses, it is possible to widen the acceptable window around Dose 2 administration without jeopardizing the primary and secondary objectives of the study. The protocol has been amended to widen the upper limit of the window around Day 57 (Dose 2) to Day 85 (ie, Day 57+28 days). Therefore, the number of additional participants necessary for inclusion in the immunogenicity subset and who would receive their second vaccination within the Day 57 window will be reduced.

For the Booster Cohort (Groups 5-6), a planned total of 60 participants will be enrolled. All participants in this cohort will be assessed for safety, reactogenicity, and immunogenicity. Participants will be randomly assigned to the 2 groups in a 5:1 ratio, ie, to a group of approximately 50 participants receiving the primary vaccine regimen (Ad26.ZEBOV followed by MVA-BN-Filo 56 days later) followed by a booster dose of Ad26.ZEBOV 4 months after Dose 2 (Group 5), or, to a placebo group of approximately 10 participants (Group 6).
These 2 additional Groups (5 and 6) have not yet been recruited. It is expected that these additional groups will likely receive their second dose in the fall of 2020, at which time it is possible that a second wave of COVID-19 may occur. The window for Dose 2 for these groups, therefore, is only being increased to 1 week to try to assure that Dose 2 is completed before a recurrence of COVID-19.
Furthermore, the window for Dose 2 for Groups 5 and 6 is limited to 1 week since this extension for the window is deemed suitable for the correct interpretation of the anamnestic response to the booster dose. If

the window for Dose 2 is further extended such that the time between Dose 2 and the booster dose is decreased, the primary response to the initial 2-dose regimen may not have reached a plateau at the time the booster dose is given and the immune system may be differently susceptible to the booster.

The participants will be randomized at baseline (Day 1) to receive the 2-dose vaccine regimen with either Ad26.ZEBOV and MVA-BN-Filo, or placebo. Randomization of the Booster Cohort (Groups 5-6) will take place once randomization of the main part of the study (Groups 1-4) has been completed. Randomization will be done by the interactive web response system (IWRS). For Groups 1-4, investigators, study site personnel (except for those with primary responsibility for study vaccine preparation and dispensing), and participants will be blinded to the study vaccine allocation until the last participant in these groups completes the 6-month post Dose 2 time point (ie, Day 237) or discontinues earlier (and the database is locked). For Groups 5-6, investigators, study site personnel (except for those with primary responsibility for study vaccine preparation and dispensing), and participants will be blinded to the study vaccine allocation until the end of the study. Only sponsor personnel not involved in the review and determination of causality of serious adverse events reported during the study will be unblinded for Groups 1-4 at the time of the primary safety and immunogenicity analyses (28 days post Dose 2 time point, see below), and for Groups 5-6 at the time of the interim analysis when all participants in the Groups 5-6 complete the 21-day post booster dose visit (or discontinue earlier).

All participants will sign the informed consent form (ICF) and will be screened for eligibility at baseline (Day 1), which is also the day of Dose 1 vaccination. If needed, the screening activities may be split over multiple visits, with a maximum time of up to 28 days between signing the ICF and Dose 1 vaccination. Dose 2 vaccination will be given on Day 57. Participants in the immunogenicity subset and in Groups 5-6 will be followed for immunogenicity until the 21-day post Dose 2 visit (Day 78). Participants in Groups 5-6 will in addition be followed up from pre booster dose (Day 177) until 12 months after receiving the booster dose (Day 537). Samples for immunogenicity assessments will be taken pre Dose 1 (Day 1), pre Dose 2 (Day 57), 21 days post Dose 2 (Day 78), and in Groups 5-6 also pre booster dose (Day 177), and 7 days (Day 184), 21 days (Day 198), 6 months (Day 357), and 12 months (Day 537) after the booster dose. All participants will complete diary cards until 7 days post each vaccination (solicited adverse events), which will be reviewed by study site personnel at the Day 57 visit (before Dose 2 vaccination), at the Day 78 visit, and at the Day 184 visits (Groups 5-6 only). Unsolicited adverse events will be recorded until 28 days post each vaccination; participants will be asked about these at the Day 57 visit, at the Day 78 visit, at the Day 177, 184 and 198 visits (Groups 5-6 only), and by means of a telephone call at Days 29, 85, and at Day 205 (Groups 5-6 only). Serious adverse events will be recorded until the end of the study with a telephone call foreseen for Groups 1-4 only at 6 months post Dose 2 (Day 237).

The investigators, together with the sponsor's medical monitor, will be responsible for the safety monitoring of the study. If at least one pre-specified pausing rule is met, administration of study vaccine will be paused. According to the sponsor's standard procedures, a multidisciplinary Safety Management Team (SMT) is in place for the development of the Ebola vaccines regimen. This SMT will monitor the safety of the participants in this study as part of its regular surveillance of all clinical studies using the Ebola vaccines Ad26.ZEBOV, MVA-BN-Filo.

PARTICIPANT POPULATION

The participant population will consist of medically stable men and women 18 to 50 years of age (inclusive), without known prior exposure to EBOV (including travel to an area with Ebola outbreak less than 1 month prior to screening, if applicable) or diagnosis of Ebola virus disease (EVD). Participants who have received a candidate Ebola vaccine or a candidate Ad26- or MVA-based vaccine in the past or with known allergy or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine products, including known allergy to chicken or egg protein and gentamicin will be excluded.

DOSAGE AND ADMINISTRATION

All participants will receive the study vaccine (Ad26.ZEBOV and MVA-BN-Filo, or placebo) administered through IM injection (0.5 mL) in the deltoid muscle:

- Ad26.ZEBOV as Dose 1 ($5x10^{10}$ vp, Lot A) on Day 1, followed by MVA-BN-Filo as Dose 2 ($1x10^{8}$ Inf U, Lot 1) on Day 57; *OR*
- Ad26.ZEBOV as Dose 1 ($5x10^{10}$ vp, Lot B) on Day 1, followed by MVA-BN-Filo as Dose 2 ($1x10^{8}$ Inf U, Lot 2) on Day 57; *OR*
- Ad26.ZEBOV as Dose 1 ($5x10^{10}$ vp, Lot C) on Day 1, followed by MVA-BN-Filo as Dose 2 ($1x10^{8}$ Inf U, Lot 3) on Day 57; *OR*
- Ad26.ZEBOV as Dose 1 ($5x10^{10}$ vp, a single Lot) on Day 1, followed by MVA-BN-Filo as Dose 2 ($1x10^{8}$ Inf U, a single Lot) on Day 57, followed by Ad26.ZEBOV ($5x10^{10}$ vp, a single Lot) as booster dose, 4 months post Dose 2 (Group 5 only); *OR*
- Placebo (0.9% saline) as Dose 1 on Day 1, followed by placebo as Dose 2 on Day 57, followed by placebo as booster dose on Day 177 (booster dose for Group 6 only).

IMMUNOGENICITY EVALUATIONS

Blood samples for humoral immunogenicity assessments will be collected from participants in the immunogenicity subset and Groups 5-6 at the time points indicated in the TIME AND EVENTS SCHEDULE.

SAFETY EVALUATIONS

All safety evaluations will be performed as specified in the TIME AND EVENTS SCHEDULE.

Safety will be assessed by collection of solicited local and systemic adverse events (reactogenicity), unsolicited adverse events, and serious adverse events. After each vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited local and systemic events, or longer if deemed necessary by the investigator. Solicited and unsolicited adverse events emerging during the observation period will be recorded in the electronic case report form (eCRF).

Upon discharge from the study site, participants will receive a thermometer (to measure body temperature), a ruler (to measure local injection site reactions), and a participant diary to record body temperature and symptoms of solicited local (at injection site) and systemic adverse events and will be trained on how to collect this information. The participants will record symptoms of solicited local and systemic adverse events in the diary in the evening after each vaccination and then daily for the next 7 days. The diary cards will be reviewed by study site personnel at the Day 57 visit (before Dose 2 vaccination), at the Day 78 visit, and at the Day 184 visit (7 days post booster dose visit, for Groups 5-6 only).

All adverse events and special reporting situations, whether serious or nonserious, that are related to study-related procedures or to non-investigational (concomitant) sponsor products, and pregnancy (if applicable), will be reported from the time a signed and dated ICF is obtained onwards.

Other serious adverse events and special reporting situations will be reported from first dose of study vaccine until the end of the study.

Other nonserious adverse events and special reporting situations will be reported from first dose of study vaccine until 28 days after first dose of study vaccine, and from the second dose of study vaccine until 28 days thereafter. Participants will be asked about the occurrence of unsolicited adverse events at the

Day 57 visit (before Dose 2 vaccination), at the Day 78 visit, and by means of a telephone call at Days 29 and 85.

Unsolicited adverse events with the onset date outside the time frame defined above (>28 days after previous study vaccination), which are ongoing on the day of the subsequent vaccination, should be recorded on the eCRF Adverse Event page.

Clinically relevant medical events occurring between signing of ICF and first vaccination will be collected on the eCRF Medical History page as pre-existing conditions.

The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Other safety assessments include vital signs (blood pressure, pulse/heart rate, and body temperature), physical examination and pregnancy testing.

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

STATISTICAL METHODS

For the main part of the study (Groups 1-4), the primary safety and immunogenicity analyses will be conducted when all participants in Groups 1-4 have completed the 28-day post Dose 2 time point or discontinued earlier, and the database has been locked. Only sponsor personnel not involved in the review and determination of causality of serious adverse events reported during the study will be unblinded to Groups 1-4 at this time point. Investigators, study site personnel (except for those with primary responsibility for study vaccine preparation and dispensing), and participants will remain blinded to the study vaccine allocation until the last participant in Groups 1-4 completes the 6-month post Dose 2 time point (ie, Day 237, last study related visit) or discontinues earlier (and the database is locked). An interim analysis will be performed when all participants in Groups 1-4 have completed the 6-month post Dose 2 visit, ie, the last study-related visit (or discontinue earlier), and the database has been locked.

For the Booster Cohort (Groups 5-6), an interim analysis will be performed when all participants in Groups 5-6 have completed the 28-day post booster dose time point (or discontinued earlier). This analysis, based on the corresponding locked database, will include all available data (including safety and 21-day post booster dose immunogenicity data) up to the cut off. Only sponsor personnel not involved in the review and determination of causality of serious adverse events reported during the study will be unblinded to Groups 5-6 at this time point. Investigators, study site personnel (except for those with primary responsibility for study vaccine preparation and dispensing), and participants will remain blinded to the study vaccine allocation until the database is locked for the final analysis.

The final analysis will be conducted when all participants in the study have completed the last study-related visit or have discontinued earlier.

A planned analysis may be combined with the subsequent analysis, if deemed necessary (eg, when the dates of 2 planned database locks are very close).

Descriptive statistics (including geometric means with their corresponding 95% CIs, median, interquartile range, minimum, maximum, as applicable) will be calculated for continuous immunologic parameters at each time point. Graphical representations of immunologic parameters will be prepared, as applicable. Frequency tabulations will be calculated for discrete (qualitative) immunologic parameters at each time point.

To assess the primary objective, each pairwise comparison (ie, Groups 1 vs 2, 1 vs 3, 2 vs 3) of the anti-EBOV GP binding antibody responses 21 days post Dose 2 vaccination with MVA-BN-Filo will be based on ratios of the GMCs with corresponding 95% CI. Equivalence of any 2 groups will be shown if the

95% CI of the estimated GMC ratio lies entirely within 0.5 and 2.0. Lot-to-lot consistency is accomplished if equivalence is shown for all 3 pairwise comparisons.

For the secondary objective, each pairwise comparison of the anti-EBOV GP binding antibody responses 56 days post Dose 1 vaccination with Ad26.ZEBOV will be based on ratios of the GMCs with corresponding 95% CI. Equivalence of any 2 groups will be shown if the 95% CI of the estimated GMC ratio lies entirely within 0.5 and 2.0. Lot-to-lot consistency (for Ad26.ZEBOV) is accomplished if equivalence is shown for all 3 pairwise comparisons.

As a sensitivity analyses, both the primary and secondary hypotheses of equivalence will also be tested based on data of participants who received the second vaccination within the original window (±3 days) around the Day 57 visit.

Safety Analyses

No formal statistical testing of safety data is planned. All the participants who received at least 1 dose of the study vaccine will be included in the safety analysis. The reporting of the categorical safety data will include the incidence, severity, relatedness, and type of adverse events. Continuous safety parameters will be descriptively analyzed (showing the mean, standard deviation, median and quartiles [Q1 and Q3]).

Baseline for all vital signs and physical examinations will be defined as the last evaluation done before Dose 1 vaccination.

TIME AND EVENTS SCHEDULE

Groups 1, 2, 3, 4, 5 and 6	Screening/Baseline [a]	Vaccination and Postvaccination Visits [b]				Follow-up
	Day 1	**Day 29 (Telephone call for safety follow-up) ±1w**	**Day 57 Groups 1-4: -3d, +28d (Day 54-85)[u] Groups 5 and 6: ±1w**	**Day 78 ±3d**	**Day 85 (Telephone call for safety follow-up) ±1w**	**Day 237[r] (Telephone call for safety follow-up) ±15d**
Study Procedures	**Dose 1**	28 days post Dose 1	**Dose 2**	21 days post Dose 2	28 days post Dose 2	6 months post Dose 2
Screening/Administrative						
Informed consent [c,t]	X					
Inclusion/exclusion criteria	X[d]					
Medical history and demographics	X					
Prestudy-specific therapies [e]	X					
Randomization	X					
Prevaccination symptoms [f]	X[g]		X[g]			
Study vaccine administration	▲		▼			
Immunogenicity Assessments						
Blood sampling for immunogenicity assays (8.5 mL per blood draw)[s] (immunogenicity subset and Groups 5-6 only)	X[g]		X[g]	X		
Safety Assessments						
Urine pregnancy test [h]	X[g]		X[g]			
Physical examination [i]	X[g]		X[g]	X		
Vital signs [j]	X[g]		X[g]			
Distribution of participant diary [k]	X		X			
Review of participant diary by study site personnel [l]			X[g]	X		
30-minute postvaccination observation [m]	X		X			

Groups 1, 2, 3, 4, 5 and 6	Screening/Baseline [a]	Vaccination and Postvaccination Visits [b]				Follow-up
	Day 1	**Day 29 (Telephone call for safety follow-up) ±1w**	**Day 57 Groups 1-4: -3d, +28d (Day 54-85)[u] Groups 5 and 6: ±1w**	**Day 78 ±3d**	**Day 85 (Telephone call for safety follow-up) ±1w**	**Day 237[r] (Telephone call for safety follow-up) ±15d**
Study Procedures	**Dose 1**	28 days post Dose 1	**Dose 2**	21 days post Dose 2	28 days post Dose 2	6 months post Dose 2
Solicited adverse events recording [n]	From Dose 1 vaccination until 7 days post Dose 1		From Dose 2 vaccination until 7 days post Dose 2			
Unsolicited adverse events recording [o,p]	From Dose 1 vaccination until 28 days post Dose 1		From Dose 2 vaccination until 28 days post Dose 2			
Pregnancy, serious adverse events [o]	Continuous					
Concomitant medications [q]	From Dose 1 vaccination until 28 days post Dose 1		From Dose 2 vaccination until 28 days post Dose 2			X[q]

▲ *Ad26.ZEBOV 5x10[10] vp or placebo* ▼ *MVA-BN-Filo 1x10[8] Inf U or placebo.*

d: days; w: week

NOTE: *If a participant withdraws early from the study, early withdrawal assessments should be obtained per the assessments for the 21-day post Dose 2 visit, with the exception of the immunogenicity assessments, if applicable. A participant who wishes to withdraw consent from participation in the study will be offered an optional visit for safety follow-up (before formal withdrawal of consent), but the participant has the right to refuse.*

In view of the COVID-19 pandemic, alternative arrangements to conduct study visits according to the protocol may be considered.

[a] Screening and signing of the informed consent form (ICF) will occur at baseline (Day 1), which is also the day of Dose 1 vaccination. If needed, the screening activities may be split over multiple visits, with a maximum time of up to 28 days between signing the ICF and Dose 1 vaccination.

[b] In addition to the assessments scheduled during the study site visits, participants will be instructed to contact the investigator before the next visit if they experience any adverse event or intercurrent illness that they perceive as relevant and/or can be possibly related to study vaccine in their opinion.

[c] Signing of the ICF needs to be done before the first study-related activity.

[d] The investigator should ensure that all study enrollment criteria have been met at the end of screening. If a participant's clinical status changes (including receipt of additional medical records) after screening but before Dose 1 vaccination such that he/she no longer meets all eligibility criteria, then the participant should be excluded from further participation in the study.

[e] Prestudy-specific therapies such as analgesic/antipyretic medications, nonsteroidal anti-inflammatory drugs, vaccines, and immunomodulators/suppressors (eg, cancer chemotherapeutic agents, systemic corticosteroids) administered up to 30 days prior to Dose 1 vaccination and previous vaccinia/smallpox vaccination at any time prior to study entry must be recorded in the electronic case report form (eCRF).

[f] The investigator must check for acute illness or body temperature ≥38.0°C at the time of vaccination. In such cases, the participant may be vaccinated up to, and no later than 10 days after the scheduled vaccination, or be withdrawn at the discretion of the investigator and after consultation with the sponsor.

[g] Prior to study vaccine administration.

[h] For women of childbearing potential.

[i] A full physical examination (excluding genito-urinary system), including height and body weight, will be carried out at screening (Day 1). At other visits, an abbreviated, symptom-directed examination will be performed as indicated by the investigator.

[j] Includes blood pressure and pulse/heart rate (at least 5 minutes of rest in supine position), and oral temperature.

[k] Participants will receive a diary to document symptoms of solicited local and systemic adverse events (reactogenicity). At Day 1, in addition to the diary, a ruler and thermometer will be distributed to each participant.

[l] The participants will complete diary cards until 7 days post each vaccination (solicited adverse events), which will be reviewed by study site personnel at the Day 57 visit (before Dose 2 vaccination) and at the Day 78 visit.

[m] After each vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions or solicited events. Solicited and unsolicited adverse events emerging during the observation period will be recorded in the eCRF.

[n] Solicited adverse events will be documented in the evening after each vaccination and then daily for the next 7 days.

[o] All adverse events and special reporting situations, whether serious or nonserious, that are related to study-related procedures or to non-investigational (concomitant) sponsor products, and pregnancy (if applicable), will be reported from the time a signed and dated ICF is obtained onwards. Other serious adverse events and special reporting situations will be reported from first dose of study vaccine until the end of the study. Other nonserious adverse events and special reporting situations will be reported from first dose of study vaccine until 28 days after first dose of study vaccine, and from the second dose of study vaccine until 28 days thereafter. Unsolicited adverse events with the onset date outside the time frame defined above (>28 days after previous study vaccination), which are ongoing on the day of the subsequent vaccination, should be recorded on the eCRF Adverse Event page.

[p] Participants will be asked about the occurrence of unsolicited adverse events at the Day 57 visit (before Dose 2 vaccination), at the Day 78 visit, and by means of a telephone call at Days 29 and 85.

[q] Concomitant therapies such as analgesic/antipyretic medications, nonsteroidal anti-inflammatory drugs, vaccines, and immunomodulators/suppressors (eg, cancer chemotherapeutic agents, systemic corticosteroids) must be recorded from Dose 1 vaccination up to 28 days post Dose 1 vaccination and from Dose 2 vaccination up to 28 days post Dose 2 vaccination. All other concomitant therapies should also be recorded beyond these time frames until the end of the study (ie, 6 months post Dose 2) if administered in conjunction with serious adverse events and pregnancies (if applicable).

[r] This is not required for participants in Groups 5-6 (Booster Cohort).

[s] Humoral immunogenicity assessments on Days 1, 57, and 78; determination of neutralizing antibodies against the Ad26 vector on Day 1 for Groups 5-6 (Booster Cohort) only.

[t] Informed consent for Groups 5-6 (Booster Cohort) includes additional procedures. See below.

[u] Lower limit: Day 57-3 days, upper limit: Day 57+28 days

Additional Visits for Groups 5-6	Booster	Vaccination and Postvaccination Visits [a]			Follow-up	
	Day 177 ±1w	Day 184 ±2d	Day 198 ±3d	Day 205 (Telephone call for safety follow-up) ±1w	Day 357 ±2w	Day 537 ±4w
Study Procedures	**Booster Dose** 4 months post Dose 2	7 days post booster dose	21 days post booster dose	28 days post booster dose	6 months post booster dose	12 months post booster dose
Screening/Administrative						
Prevaccination symptoms [b]	X					
Study vaccine administration	▲					
Immunogenicity Assessments						
Blood sampling for immunogenicity assays (8.5 mL per blood draw)[c]	X[d]	X	X		X	X
Safety Assessments						
Urine pregnancy test [e]	X[d]					
Physical examination [f]	X[d]	X[f]	X[f]			
Vital signs [g]	X[d]	X[g]	X[g]			
Distribution of participant diary [h]	X					
Review of participant diary by study site personnel [i]		X				
30-minute postvaccination observation[j]	X					
Solicited adverse events recording [k]	From booster vaccination until 7 days post booster					
Unsolicited adverse events recording [l,m]	From booster vaccination until 28 days post booster					
Pregnancy, serious adverse events [l]	Continuous					
Concomitant medications [n]	From booster vaccination until 28 days post booster				X[n]	

▲ *Ad26.ZEBOV 5x10^{10} vp*

d: days; w: week

[a] In addition to the assessments scheduled during the study site visits, participants will be instructed to contact the investigator before the next visit if they experience any adverse event or intercurrent illness that they perceive as relevant and/or can be possibly related to study vaccine in their opinion.

[b] The investigator must check for acute illness or body temperature ≥38.0°C at the time of vaccination. In such cases, the participant may be vaccinated up to, and no later than 10 days after the scheduled vaccination or be withdrawn at the discretion of the investigator and after consultation with the sponsor.

[c] Humoral immunogenicity assessments on Days 177, 184, 198, 357 and 537; assessment of neutralizing antibodies against the Ad26 vector on Days 177 and 198.

[d] Prior to study vaccine administration.

[e] For women of childbearing potential.

[f] An abbreviated, symptom-directed examination will be performed as indicated by the investigator.

[g] Includes blood pressure and pulse/heart rate (at least 5 minutes of rest in supine position), and oral temperature.

[h] Participants will receive a diary to document symptoms of solicited local and systemic adverse events (reactogenicity).

[i] The participants will complete diary cards until 7 days post each vaccination (solicited adverse events), which will be reviewed by study site personnel at the Day 184 visit.

[j] After each vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions or solicited events. Solicited and unsolicited adverse events emerging during the observation period will be recorded in the eCRF.

[k] Solicited adverse events will be documented in the evening after each vaccination and then daily for the next 7 days.

[l] All adverse events and special reporting situations, whether serious or nonserious, that are related to study-related procedures or to non-investigational (concomitant) sponsor products, and pregnancy (if applicable), will be reported from the time a signed and dated ICF is obtained onwards. Other serious adverse events and special reporting situations will be reported from first dose of study vaccine until the end of the study. Other nonserious adverse events and special reporting situations will be reported from first dose of study vaccine until 28 days after booster dose of study vaccine.

[m] Participants will be asked about the occurrence of unsolicited adverse events at the Day 177 visit (before booster dose vaccination), Day 184 and Day 198 visits and by means of a telephone call at Day 205.

[n] Concomitant therapies such as analgesic/antipyretic medications, nonsteroidal anti-inflammatory drugs, vaccines, and immunomodulators/suppressors (eg, cancer chemotherapeutic agents, systemic corticosteroids) must be recorded from booster dose vaccination up to 28 days post booster dose vaccination. All other concomitant therapies should also be recorded beyond these time frames until the end of the study if administered in conjunction with serious adverse events and pregnancies (if applicable).

ABBREVIATIONS

Ad26	Adenovirus serotype 26
Ad26.ZEBOV	Adenovirus serotype 26 encoding the Ebola virus Mayinga glycoprotein
β-hCG	β-human chorionic gonadotropin
BN	Bavarian Nordic
CI	confidence interval
COVID-19	coronavirus disease 2019
EBOV	Ebola virus
eCRF	electronic case report form
eDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EU/ml	ELISA unit/ml
EVD	Ebola virus disease
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMP	Good Manufacturing Practice
GP	glycoprotein
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDT	IDT Biologika GmbH in Dessau-Rosslau, Germany
IEC	Independent Ethics Committee
IM	intramuscular(ly)
Inf U	infectious unit(s)
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
kb	kilobase
MARV	Marburg virus
MedDRA	Medical Dictionary for Regulatory Activities
MVA	Modified Vaccinia Ankara
MVA-BN-Filo	Modified Vaccinia Ankara Bavarian Nordic vector expressing multiple filovirus proteins
NHP	nonhuman primate(s)
NP	nucleoprotein
PCR	polymerase chain reaction
PQC	Product Quality Complaint
PREVAC	Partnership for Research on Ebola Vaccination
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMT	Safety Management Team
SUDV	Sudan virus
SUSAR	suspected unexpected serious adverse reaction
TAFV	Tai Forest virus
VISP	vaccine-induced seropositivity
vp	viral particle(s)
vs	versus
WHO	World Health Organization

DEFINITIONS OF TERMS

Study vaccine	Ad26.ZEBOV, MVA-BN-Filo, or placebo
Independent study vaccine monitor	An unblinded study vaccine monitor assigned to the study who is responsible for the unblinded interface between the sponsor and the study site pharmacy.
Solicited adverse events (reactogenicity)	Local (at injection site) and systemic adverse events that are common and known to occur after vaccination and that are usually collected in a standard, systematic format in vaccine clinical studies. For the list of solicited adverse events in this study, see Section 9.3. For the purpose of vaccine clinical studies, all other adverse events are considered unsolicited; however, this definition should be distinguished from definitions based on pharmacovigilance guidelines.
Immunogenicity subset	A subset of 456 participants in Groups 1-4 (144 in each of Groups 1 to 3 and 24 in Group 4) that will be assessed for immunogenicity.

Study Naming Convention

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

1. INTRODUCTION

Janssen Vaccines & Prevention B.V. (hereafter referred to as the sponsor), in collaboration with Bavarian Nordic GmbH (BN), is investigating the potential of a prophylactic Ebola vaccine regimen (VAC52150) comprised of the following 2 candidate Ebola vaccines:

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

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

For the most comprehensive nonclinical and clinical information regarding Ad26.ZEBOV and MVA-BN-Filo, refer to the latest versions of the Investigator's Brochures (IB) and Addenda.[3,4] A brief summary of the clinical information available at the time of the protocol writing is provided below.

The term "study vaccine" throughout the protocol, refers to study vaccine (Ad26.ZEBOV, MVA-BN-Filo), or placebo.

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 (EVD), which can induce severe hemorrhagic fever in humans and nonhuman primates (NHP). Case fatality rates in Ebola disease range from 25% to 90% (average: 50%), according to the World Health Organization (WHO).[6] These viruses are highly prioritized by the United States Government, who has defined them as 'Category A' agents, due to the high mortality rate of infected individuals. Currently, no cure exists and no vaccine has been licensed in Europe or the United States for this disease.

Filoviruses are named for their long, filamentous shape. Within this filamentous virus, a single 19-kilobase (kb) negative-sense 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.[2]

In this Phase 3 study, the sponsor's adenovirus serotype 26 (Ad26) vector expressing the EBOV Mayinga GP (Ad26.ZEBOV) and the MVA-BN vector with EBOV, SUDV, and MARV GP and TAFV NP inserts (MVA-BN-Filo) will be evaluated as a heterologous 2-dose vaccine regimen, in

which one study vaccine (Ad26.ZEBOV) is used to induce an EBOV-specific immune response and the other study vaccine (MVA-BN-Filo), administered 56 days later, is used to enhance the immune response. The EBOV GP that circulated in West Africa during the 2014-2016 epidemic had 97% homology with the EBOV GP used in this vaccine regimen.[1]

For an overview of the nonclinical studies with Ad26.ZEBOV and MVA-BN-Filo, refer to the respective IBs.[3,4]

Clinical Studies

The safety, reactogenicity, and immunogenicity of the Ad26.ZEBOV and MVA-BN-Filo vaccines are being evaluated in a number of completed and ongoing clinical studies in adults and children ≥1 year of age. The sponsor's current clinical development plan contains 4 completed Phase 1 studies (EBL1001, EBL1002, EBL1003, and EBL1004), the ongoing Phase 1 study EBL1007, 1 completed Phase 2 study (EBL2001), 3 ongoing Phase 2 studies (EBL2002, EBL2003, and EBL2004/Partnership for Research on Ebola Vaccination [PREVAC]), 2 completed Phase 3 studies (EBL3002 and EBL3003) and 3 ongoing Phase 3 studies (EBL3001, EBL3005, and EBL4001). A planned Phase 2 study (EBL2005) will evaluate the safety and immunogenicity of the vaccine regimen in infants aged 4-11 months. In addition, 2 Phase 2 studies in adult health care and frontline workers in Africa (EBL2007 and EBL2009) and 2 Phase 3 studies (EBL3008 [vaccine deployment in the Democratic Republic of the Congo] and EBL3009 [vaccination of sponsor employees in case of deployment in high-risk situations]) are planned. An additional Phase 1 study with the multivalent vaccine VAC69120FLV1001 has been completed, where a group receiving Ad26.ZEBOV, MVA-BN-Filo in a 56-day interval was included as a control arm. The data from this control arm support the safety and immunogenicity of the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen in a 56-day interval.

As of 19 April 2019, an estimated 6,800 participants (estimation based on randomization ratios) have received at least the Dose 1 vaccination (Ad26.ZEBOV, MVA-BN-Filo, or placebo/active comparator), including approximately 1,800 children (1-17 years of age) and 400 human immunodeficiency virus (HIV)+ adults who have been vaccinated.

Refer to the latest versions of the Ad26.ZEBOV and MVA-BN-Filo IBs and Addenda for more details.[3,4] A summary is provided below.

Phase 1 Studies

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

Both vaccines are well tolerated, with no safety concerns identified. Reactogenicity was slightly more commonly reported among participants following Ad26.ZEBOV than following MVA-BN-Filo vaccination. The most frequently reported solicited adverse events reported in the

4 individual Phase 1 studies were injection site pain, injection site warmth, fatigue, headache, and myalgia. The most frequently reported unsolicited adverse events were hypokalemia, neutropenia, and neutrophil count decreased.

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

Phase 2/3 Studies

In the ongoing, randomized, controlled Phase 2/3 studies, enrollment of both adults and children is complete. The safety data from 5 Phase 2/3 studies (EBL2001, EBL2002, EBL3001, EBL3002, and EBL3003) were unblinded to the group level in response to the May 2018 outbreak in the Democratic Republic of the Congo. The serious adverse event databases have been reconciled and include, in addition to the studies listed below, serious adverse event data from EBL2004/PREVAC.

In general, the vaccine regimen of Ad26.ZEBOV followed by MVA-BN-Filo 56 days later was well tolerated and no safety signals were identified. The majority of solicited adverse events were of mild or moderate intensity after vaccination with Ad26.ZEBOV or MVA-BN-Filo. The frequency of grade 3 pyrexia (≥39.0 C) was less than 1% following vaccination and the incidence of any febrile response was less than 7.5% in any group. As expected, the frequency of local and systemic reactogenicity was more common in healthy adult participants who received active vaccine compared to placebo and was similar to the incidence reported in the Phase 1 studies. Reactogenicity was also slightly more commonly reported among participants following Ad26.ZEBOV than following MVA-BN-Filo vaccination which was also noted in the Phase 1 studies.

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

In the ongoing clinical studies with Ad26.ZEBOV, there have been a few reports of mild to moderate paresthesia especially in the hands and feet or a sensation of mild to moderate muscle weakness in participants vaccinated with Ad26.ZEBOV or placebo. These symptoms have been observed to last no more than 24 to 48 hours in the majority of cases but can last for several weeks before resolving spontaneously. These types of symptoms have been reported following administration of other licensed vaccines and following acute viral infections of various types. One serious adverse event of probable peripheral sensory neuropathy (nerve damage that may

cause tingling, numbness, pain, or loss of pain sensation) of moderate severity has occurred and has been ongoing for several months, interfering with some of the participant's daily activities (for details, refer to the Ad26.ZEBOV IB, Edition 6).[3]

The Phase 2/3 studies confirm the immunogenicity of the Ad26.ZEBOV, MVA-BN-Filo regimen.

1.2. Benefit/Risk Section

1.2.1. Known Benefits

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

1.2.2. Potential Benefits

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

1.2.3. Known Risks

The safety, reactogenicity, and immunogenicity of the Ad26.ZEBOV and MVA-BN-Filo vaccines are being evaluated in a number of completed and ongoing clinical studies in adults and children ≥1 year of age. Both vaccines are well tolerated, with no safety concerns identified. The vaccines mainly elicited some symptoms of solicited local and systemic reactions, as expected with injectable vaccines, and no serious safety concerns in participants. MVA-BN-based vaccines have been administered to more than 13,300 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 are specified in the protocol and will be monitored during the study.

Risks Related to Vaccination

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

Participants may exhibit general signs and symptoms associated with administration of a vaccine, including fever, chills, rash, myalgia, nausea/vomiting, headache, dizziness, arthralgia, general itching, and fatigue. These side effects will be monitored, but are generally short-term and do not require treatment.

Syncope can occur in association with administration of injectable vaccines and syncope can be accompanied by falls. Procedures should be in place to avoid falling injury. If syncope develops, participants should be observed until the symptoms resolve. Fear of injection might lead to fainting and fast breathing.

Participants may have an allergic reaction to the vaccination. An allergic reaction may cause a rash, urticaria, or anaphylaxis. Severe reactions are rare. Medications must be available in the clinic to treat serious allergic reactions. Participants with a known allergy, or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine products (including any of the constituents of the study vaccine) will be excluded from the study.

Risks From Blood Draws

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

Vaccine-Induced Seropositivity

In general, uninfected participants who are taking part in Ebola vaccine studies may develop Ebola-specific antibodies as a result of an immune response to the candidate Ebola vaccine, referred to as vaccine-induced seropositivity (VISP). These antibodies may be detected in Ebola serologic tests, causing the test to appear positive even in the absence of actual Ebola infection. VISP may become evident during the study, or after the study has been completed. The potential of a participant becoming PCR-positive after vaccination was assessed in study VAC52150EBL1002. None of the participants tested positive for EBOV after vaccination.

Consent will be obtained to contact the doctors that the participant sees regularly, to let them know that the participant is taking part in this study. It is important for all of the participant's doctors to know that the participant may be administered experimental vaccines. Participants will be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study (see Section 12.3.1).

Pregnancy and Birth Control

The effect of the vaccines on a fetus or nursing baby is unknown. Female participants of childbearing potential will be required to agree to use birth control for sexual intercourse beginning 28 days prior to vaccination and continuing until at least 3 months post Dose 1 vaccination, 28 days post Dose 2 vaccination, or 3 months post booster vaccination (Groups 5-6 only), whichever comes later. Women who are pregnant or breast-feeding may not receive further study vaccines but may continue other study procedures at the discretion of the investigator.

Male participants should inform the investigator and the sponsor in case their partner would become pregnant during the study.

Unknown Risks

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

1.2.5. Overall Benefit/Risk Assessment

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

- To date, safety data from the studies in the clinical development program revealed no significant safety issues (see Section 1.1). Further experience from Ad26.ZEBOV or MVA-BN-Filo will be gained from currently ongoing clinical studies.
- Only participants who meet all inclusion criteria and none of the exclusion criteria (specified in Section 4) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study.
- Several safety measures are included in this protocol to minimize the potential risk to participants, including the following:
  - Participants will remain under observation at the study site for at least 30 minutes after each vaccination for presence of any acute reactions and solicited events, or longer if deemed necessary by the investigator (eg, in case of grade 3 adverse events). Refer to Section 6 for more information on emergency care.
  - Safety evaluations (physical examinations and vital sign measurements) will be performed at scheduled visits during the study, as indicated in the TIME AND EVENTS SCHEDULE.
  - The investigator or clinical designee will document unsolicited adverse events as indicated in Section 12.3.1.
  - Any clinically significant abnormalities (including those persisting at the end of the study/early withdrawal) will be followed by the investigator until resolution or until a clinically stable endpoint is reached.
  - There are pre-specified pausing rules for all participants, that would result in pausing of further vaccination if predefined conditions occur, preventing exposure of new participants to study vaccine until the sponsor reviews all safety data (see Section 9.3.2).
  - Participants will discontinue study vaccine for the reasons included in Section 10.2.
  - If acute illness (excluding minor illnesses such as diarrhea or mild upper respiratory tract infection) or fever (body temperature ≥38.0°C) occur at the scheduled time for vaccination, the participant may be vaccinated up to 10 days beyond the window allowed for the scheduled vaccination, or be withdrawn from that vaccination at the discretion of the investigator and after consultation with the sponsor (see Section 6.1).
  - Contraindications to Dose 2 and booster dose vaccination are included in Section 6.2.

1.3. Overall Rationale for the Study

This Phase 3 study aims to show lot-to-lot consistency of the vaccine regimen by demonstrating that paired 2-dose vaccine regimens from 3 consecutively manufactured lots of Ad26.ZEBOV drug product (Dose 1) and 3 consecutively manufactured lots of MVA-BN-Filo drug product (Dose 2) elicit equivalent humoral immune responses. The 3 consecutive lots are Lots A, B, and C for Ad26.ZEBOV and Lots 1, 2, and 3 for MVA-BN-Filo and these lots will be compared in

3 different groups (ie, A:1 [Group 1], B:2 [Group 2], and C:3 [Group 3]) (see Section 3.1, Table 1). The results of this study will also aid in increasing the size of the overall safety and immunogenicity data packages to support approval of the Ad26.ZEBOV, MVA-BN-Filo 2-dose vaccine regimen by a regulatory authority.

Administration of a booster dose of Ad26.ZEBOV given at 1- and 2 years post Dose 1 in studies VAC52150EBL1002, VAC52150EBL2002, and VAC52150EBL3001 induced a rapid and robust anamnestic response to the booster vaccine. Administration of a booster dose in anticipation of imminent exposure to Ebola (ie, prior to deployment to an Ebola outbreak area) may be desired as a precautionary measure to optimize protection. However, there is currently no clinical data available on the immunogenicity and safety of such an Ad26.ZEBOV booster dose when administered less than 1 year after the primary vaccine regimen. Booster doses as early as 2-3 months after Dose 2 were assessed in a multivalent filovirus and an HIV vaccine program and were able to induce a marked increase in antibody concentrations, although to a lower magnitude than a later booster. Furthermore, based on the kinetics of decrease in antibody concentrations after the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen, supported by a mechanistic model of antibody persistence and general vaccine knowledge, an Ad26.ZEBOV booster dose administered from 4 months after completion of the primary vaccine regimen is likely to induce a strong anamnestic response based on mature immune memory and to maximize the likelihood of protection in case of imminent risk of exposure to Ebola. Therefore, a separate Booster Cohort of participants will receive the primary vaccine regimen followed by a booster dose of Ad26.ZEBOV 4 months after Dose 2. The participants in this Booster Cohort (Groups 5-6) will be assessed for safety and immunogenicity.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESES

2.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate that the paired 2-dose vaccine regimens from 3 consecutively manufactured lots of Ad26.ZEBOV as Dose 1 and 3 consecutively manufactured lots of MVA-BN-Filo as Dose 2, administered at a 56-day interval, induce an equivalent humoral immune response.	• Binding antibody levels against the EBOV GP using enzyme-linked immunosorbent assay (ELISA, ELISA units/mL [EU/mL]) at 21 days post Dose 2 vaccination.
Secondary	
• To demonstrate that 3 consecutively manufactured lots of Ad26.ZEBOV as Dose 1 induce an equivalent humoral immune response.	• Binding antibody levels against the EBOV GP using ELISA (EU/mL) at 56 days post Dose 1 vaccination.
• To assess the safety and reactogenicity of a heterologous 2-dose vaccine regimen of Ad26.ZEBOV and MVA-BN-Filo administered IM on Days 1 and 57, respectively, using 3 different lots of	• Solicited local and systemic adverse events until 7 days post each vaccination. • Unsolicited adverse events until 28 days post each vaccination.

Objectives	Endpoints
Ad26.ZEBOV and 3 different lots of MVA-BN-Filo.	• Serious adverse events until the end of the study.
Exploratory (Booster Cohort only)	
• To assess the humoral immune response to a booster dose of Ad26.ZEBOV given 4 months after Dose 2.	• Binding antibody levels against the EBOV GP using ELISA (EU/mL) at pre booster (Day 177) and several post booster timepoints (7-days, 21-days, 6-months and 12-months post booster dose).
• To assess the safety and reactogenicity of a booster dose of Ad26.ZEBOV.	• Solicited local and systemic adverse events until 7 days post booster vaccination. • Unsolicited adverse events until 28 days post booster vaccination. • Serious adverse events until the end of the study.
• To assess the presence of neutralizing antibodies against the Ad26 vector.	• Viral neutralizing antibody levels against the Ad26 vector at baseline, pre booster vaccination (Day 177), and at 21 days post booster vaccination.

Refer to Section 9 for evaluations related to endpoints.

2.2. Hypotheses

2.2.1. Primary Hypotheses

Null Hypothesis:

Three consecutive lots of Ad26.ZEBOV (Lots A, B, and C) as Dose 1 paired sequentially in 3 groups with 3 consecutive lots of MVA-BN-Filo (Lots 1, 2, and 3) as Dose 2 do not induce equivalent geometric mean concentrations (GMCs) of the EBOV GP-specific antibody response 21 days post Dose 2, for at least one pairwise comparison.

Alternative Hypothesis:

Three consecutive lots of Ad26.ZEBOV (Lots A, B, and C) as Dose 1 paired sequentially in 3 groups with 3 consecutive lots of MVA-BN-Filo (Lots 1, 2, and 3) as Dose 2 induce equivalent GMCs of the EBOV GP-specific antibody response 21 days post Dose 2, for all 3 pairwise comparisons (ie, Groups 1 versus [vs] 2, 1 vs 3 and 2 vs 3 [see schematic overview of the study and groups in Section 3.1, Table 1]).

Equivalence of any 2 groups (Ad26.ZEBOV as Dose 1 followed by MVA-BN-Filo as Dose 2) will be shown if the 95% confidence interval [CI] of the estimated GMC ratio lies entirely within 0.5 and 2.0. These equivalence limits were chosen primarily based on the population variability as measured by the ELISA assay. Immunogenic equivalence of the 3 different lots of Ad26.ZEBOV (Lots A, B, and C) paired sequentially in 3 groups with 3 different lots of MVA-BN-Filo (Lots 1, 2, and 3) is established if equivalence is shown for all 3 pairwise comparisons.

2.2.2. Secondary Hypotheses

The secondary hypotheses will be tested on the EBOV GP-specific antibody response 56 days post Dose 1. Similar null and alternative hypotheses will be formulated and tested using the same criteria as outlined for the primary hypotheses.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase 3 study to evaluate lot-to-lot consistency of the manufacturing process by assessing the immunogenicity of the final product of 3 consecutively manufactured lots of Ad26.ZEBOV at a nominal dose of $5x10^{10}$ viral particles (vp) as Dose 1 and 3 consecutively manufactured lots of MVA-BN-Filo at a nominal dose of $1x10^{8}$ infectious units (Inf U) as Dose 2 at a 56-day interval in adult participants (Groups 1-4). Once randomization of this part of the study is finished, an additional Booster Cohort of 60 participants will be enrolled in a 5:1 active:placebo ratio. These participants will be given the 2-dose heterologous vaccine regimen Ad26.ZEBOV (at a nominal dose of $5x10^{10}$ vp) followed by MVA-BN-Filo (at a nominal dose of $1x10^{8}$ Inf U) 56 days later, and a booster dose of Ad26.ZEBOV (at a nominal dose of $5x10^{10}$ vp) 4 months after Dose 2, or placebo (Groups 5-6).

The 3 consecutive Ad26.ZEBOV drug product lots that will be used in the study have been manufactured at the final manufacturing site (ie, IDT Biologika GmbH in Dessau-Rosslau, Germany [IDT]) and are representative of the final manufacturing process and scale (Lots A, B, and C). The 3 consecutive MVA-BN-Filo drug product lots that will be used have been manufactured at the final manufacturing site (IDT) and are representative of the final manufacturing process and scale (Lots 1, 2, and 3). Lots A, B, and C and Lots 1, 2, and 3 are paired sequentially in 3 groups (ie, A:1 [Group 1], B:2 [Group 2], and C:3 [Group 3]) of the study. Group 4 will receive 2 placebo vaccinations.

In the main part of the study (Groups 1-4), a planned total number of at least 741 participants will be enrolled. All participants in this part of the study will be assessed for safety and reactogenicity; 456 participants (144 in each of Groups 1 to 3 and 24 in Group 4) will be assessed for immunogenicity (immunogenicity subset). Participants will be randomly assigned to one of 4 groups in a 6:6:6:1 ratio, ie, to one of the 3 groups receiving Ad26.ZEBOV and MVA-BN-Filo (Groups 1 to 3) with a total of at least 234 participants per group, or to a placebo group (Group 4) with 39 participants, and the first 456 participants belonging to the immunogenicity subset.

Due to the recent (on 11 March 2020) WHO declared COVID-19 pandemic, a potential higher dropout rate (ie, higher than 5%) may occur. In addition, some participants in the immunogenicity subset may be excluded from primary immunogenicity equivalence testing because of:

- Participant not receiving Dose 2; *OR*
- Participant receiving Dose 2 outside the protocol-defined window; *OR*
- Participant not attending the 21-day post Dose 2 visit; *OR*

- Participant attending the 21-day post Dose 2 visit outside the protocol-defined window.

To mitigate these issues, additional participants may be recruited in the immunogenicity subset.

Shortly after participants received Dose 1 vaccination, 'stay-at-home' orders were imposed in the areas where the sites were located. Although the sites had implemented appropriate safety measures to prevent spread of SARS-CoV-2, approximately 22% of participants did not return to the site within the protocol defined windows (±3 days) for Dose 2 administration. Investigators were instructed to bring participants back to the site to complete the vaccine regimen, even if they were out of window. Currently, the stay-at-home orders have been lifted and participants are now able to return to the sites for follow-up. In order to reduce the number of additional participants needed for the primary and secondary immunogenicity analyses, it is possible to widen the acceptable window around Dose 2 administration without jeopardizing the primary and secondary objectives of the study. The protocol has been amended to widen the upper limit of the window around Day 57 (Dose 2) to Day 85 (ie, Day 57+28 days). Therefore, the number of additional participants necessary for inclusion in the immunogenicity subset and who would receive their second vaccination within the Day 57 window will be reduced.

For the Booster Cohort (Groups 5-6), a planned total of 60 participants will be enrolled. All participants in this cohort will be assessed for safety, reactogenicity, and immunogenicity. Participants will be randomly assigned to the 2 groups in a 5:1 ratio, ie, to a group of approximately 50 participants receiving the primary vaccine regimen (Ad26.ZEBOV followed by MVA-BN-Filo 56 days later) followed by a booster dose of Ad26.ZEBOV 4 months after Dose 2 (Group 5), or, to a placebo group of approximately 10 participants (Group 6).
These 2 additional Groups (5 and 6) have not yet been recruited. It is expected that these additional groups will likely receive their second dose in the fall of 2020, at which time it is possible that a second wave of COVID-19 may occur. The window for Dose 2 for these groups, therefore, is only being increased to 1 week to try to assure that Dose 2 is completed before a recurrence of COVID-19.
Furthermore, the window for Dose 2 is limited to 1 week so as not to impact analysis of the anamnestic response to the booster dose. If the window for Dose 2 is further extended such that the time between Dose 2 and the booster dose is decreased, the primary response to the initial 2-dose regimen may not have reached a plateau at the time the booster dose is given. In that event, it would be difficult to distinguish the primary response from the anamnestic response. To avoid this possibility, the window for Dose 2 is limited to 1 week.

The participant population will consist of medically stable men and women 18 to 50 years of age (inclusive), without known prior exposure to EBOV (including travel to an area with Ebola outbreak less than 1 month prior to screening, if applicable) or diagnosis of EVD. Participants who have received a candidate Ebola vaccine or a candidate Ad26- or MVA-based vaccine in the past or with known allergy or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine products, including known allergy to chicken or egg protein and gentamicin will be excluded.

The participants will be randomized at baseline (Day 1) to receive the 2-dose vaccine regimen with either Ad26.ZEBOV and MVA-BN-Filo, or placebo. Randomization of the Booster Cohort (Groups 5-6) will take place once randomization of the main part of the study (Groups 1-4) has been completed. Randomization will be done by the interactive web response system (IWRS).

A schematic overview of the study design and groups is provided in Table 1. For Groups 1-4, investigators, study site personnel (except for those with primary responsibility for study vaccine preparation and dispensing), and participants will remain blinded to the study vaccine allocation until the last participant in these groups completes the 6-month post Dose 2 time point (ie, Day 237) or discontinues earlier (and the database is locked). For Groups 5-6, investigators, study site personnel (except for those with primary responsibility for study vaccine preparation and dispensing), and participants will be blinded until the end of the study. Only sponsor personnel not involved in the review and determination of causality of serious adverse events reported during the study will be unblinded for Groups 1-4 at the time of the primary safety and immunogenicity analyses (28 days post Dose 2 time point, see below), and for Groups 5-6 at the time of the interim analysis when all participants in Groups 5-6 have completed the 28-day post booster dose timepoint (or discontinued earlier).

Table 1: Schematic Overview of Study Design and Groups

Groups	N	Dose 1	Dose 2	Booster Dose
		Day 1	Day 57	Day 177
1	234	Ad26.ZEBOV – Lot A	MVA-BN-Filo – Lot 1	
2	234	Ad26.ZEBOV – Lot B	MVA-BN-Filo – Lot 2	
3	234	Ad26.ZEBOV – Lot C	MVA-BN-Filo – Lot 3	
4	39	Placebo	Placebo	
5	50	Ad26.ZEBOV[a]	MVA-BN-Filo[b]	Ad26.ZEBOV[a]
6	10	Placebo	Placebo	Placebo

N: number of participants to receive study vaccine.
Ad26.ZEBOV dose level is $5x10^{10}$ vp and MVA-BN-Filo dose level is $1x10^{8}$ Inf U, placebo is 0.9% saline.
[a,b] Actual lots to be determined later

All participants will receive the study vaccine (Ad26.ZEBOV and MVA-BN-Filo, or placebo) administered through IM injection (0.5 mL) in the deltoid muscle:

- Ad26.ZEBOV as Dose 1 ($5x10^{10}$ vp, Lot A) on Day 1, followed by MVA-BN-Filo as Dose 2 ($1x10^{8}$ Inf U, Lot 1) on Day 57; *OR*
- Ad26.ZEBOV as Dose 1 ($5x10^{10}$ vp, Lot B) on Day 1, followed by MVA-BN-Filo as Dose 2 ($1x10^{8}$ Inf U, Lot 2) on Day 57; *OR*
- Ad26.ZEBOV as Dose 1 ($5x10^{10}$ vp, Lot C) on Day 1, followed by MVA-BN-Filo as Dose 2 ($1x10^{8}$ Inf U, Lot 3) on Day 57; *OR*
- Ad26.ZEBOV as Dose 1 ($5x10^{10}$ vp, a single Lot) on Day 1, followed by MVA BN Filo as Dose 2 ($1x10^{8}$ Inf U, a single Lot) on Day 57, followed by Ad26.ZEBOV ($5x10^{10}$ vp, a single Lot) as booster dose, 4 months post Dose 2 (Group 5 only); *OR*
- Placebo (0.9% saline) as Dose 1 on Day 1, followed by placebo as Dose 2 on Day 57, followed by placebo as booster dose on Day 177 (booster dose for Group 6 only).

All participants will sign the informed consent form (ICF) and will be screened for eligibility at baseline (Day 1), which is also the day of Dose 1 vaccination. If needed, the screening activities

may be split over multiple visits, with a maximum time of up to 28 days between signing of the ICF and Dose 1 vaccination. Dose 2 vaccination will be given on Day 57. Participants in the immunogenicity subset and in Groups 5-6 will be followed for immunogenicity until the 21-day post Dose 2 visit (Day 78). Participants in Groups 5-6 will in addition be followed up from pre booster dose (Day 177) until 12 months after receiving the booster dose (Day 537). Samples for immunogenicity assessments will be taken pre Dose 1 (Day 1), pre Dose 2 (Day 57), 21 days post Dose 2 (Day 78), and in Groups 5-6 also pre booster dose (Day 177), and 7 days (Day 184), 21 days (Day 198), 6 months (Day 357), and 12 months (Day 537) after the booster dose. All participants will complete diary cards until 7 days post each vaccination (solicited adverse events), which will be reviewed by study site personnel at the Day 57 visit (before Dose 2 vaccination), at the Day 78 visit, and at the Day 184 visit (Groups 5-6 only). Unsolicited adverse events will be recorded until 28 days post each vaccination; participants will be asked about these at the Day 57 visit, at the Day 78 visit, at the Day 177, 184 and 198 visits (Groups 5-6 only), and by means of a telephone call at Days 29 and 85, and at Day 205 (Groups 5-6 only). Serious adverse events will be recorded until the end of the study with a telephone call foreseen for Groups 1-4 only at 6 months post Dose 2 (Day 237).

For the main part of the study (Groups 1-4), the primary safety and immunogenicity analyses will be performed when all participants in the main part of the study (Groups 1-4) have completed the 28-day post Dose 2 time point or discontinued earlier, and the database is locked. Only sponsor personnel not involved in the review and determination of causality of serious adverse events reported during the study will be unblinded to Groups 1-4 at this time point. An interim analysis will be performed when all participants in Groups 1-4 have completed the 6-month post Dose 2 visit, ie, the last study-related visit (or discontinue earlier), and the database has been locked.

For the Booster Cohort (Groups 5-6), an interim analysis will be performed when all participants in Groups 5-6 have completed 28-day post booster dose time point (or discontinued earlier). This analysis, based on the corresponding locked database, will include all available data (including safety and 21-day post booster dose immunogenicity data) up to the cut off. Only sponsor personnel not involved in the review and determination of causality of serious adverse events reported during the study will be unblinded to Groups 5-6 at this time point.

The final analysis will be performed when all participants in the study have completed the last study-related visit or have discontinued earlier (and the database is locked).

A planned analysis may be combined with the subsequent analysis, if deemed necessary (eg, when the dates of 2 planned database locks are very close).

The study is considered completed when the last participant has completed the last study procedure.

The investigators, together with the sponsor's medical monitor, will be responsible for the safety monitoring of the study. If at least one pre-specified pausing rule is met, administration of study vaccine will be paused (see Section 9.3.2 for details). As per Janssen standard procedures, a multidisciplinary Safety Management Team (SMT) is in place for the development of the Ebola

vaccines regimen. This SMT will monitor the safety of the participants in this study as part of its regular surveillance of all clinical studies using the Ebola vaccines Ad26.ZEBOV, MVA-BN-Filo (see Section 9.3.1 for details).

3.2. Study Design Rationale

Control and Blinding

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

Vaccination Groups

Groups 1, 2, and 3 will only differ in the lots of the study vaccine, while the dose of each vaccine and the sequence of vaccination will be identical. For Groups 1, 2, 3 and 5, Dose 1 consists of Ad26.ZEBOV at a nominal dose of $5x10^{10}$ vp and Dose 2 consists of MVA-BN-Filo at a nominal dose of $1x10^{8}$ Inf U. For Group 5, the booster dose consists of Ad26.ZEBOV at a nominal dose of $5x10^{10}$ vp from a single lot. Groups 4 and 6 will receive placebo.

4. PARTICIPANT POPULATION

Screening for eligible participants will be performed at baseline (Day 1), which is also the day of Dose 1 vaccination. If needed, the screening activities may be split over multiple visits, with a maximum time of up to 28 days between signing of the ICF and Dose 1 vaccination.

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

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

4.1. Inclusion Criteria

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

1. Signed an ICF indicating that he or she understands the purpose of, and procedures required for, the study as well as the potential risks and benefits of the study, and is willing to participate in the study.

2. Man or woman, 18 to 50 years of age, inclusive, on the day of signing the ICF.

3. Medically stable in the investigator's clinical judgment on the basis of physical examination, medical history, and vital signs performed at screening.

4. Criterion modified per Amendment 2

   4.1 Before randomization, a woman must be either:

   a. Not of childbearing potential;

   b. Of childbearing potential and practicing an acceptable effective method of birth control and agrees to remain on such a method of birth control from signing the ICF until at least 3 months post Dose 1 vaccination or 28 days post Dose 2 vaccination or 3 months post booster vaccination (Groups 5-6 only), whichever comes later. Use of hormonal contraception should start at least 28 days before the first administration of study vaccine. Acceptable effective methods for this study include:

      1) hormonal contraception;
      2) intrauterine device (IUD);
      3) intrauterine hormone-releasing system (IUS);
      4) male or female condom with or without spermicide;
      5) cap, diaphragm, or sponge with a vaginal spermicide;
      6) vasectomized partner (the vasectomized partner should be the sole partner for that participant);
      7) sexual abstinence*.

         Sexual abstinence is considered an effective method **only if defined as refraining from heterosexual intercourse from signing the ICF until at least 3 months post Dose 1 vaccination or 28 days post Dose 2 vaccination, whichever comes later. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

5. Women of childbearing potential must have a negative urine β-hCG pregnancy test at screening and immediately prior to each study vaccine administration.

6. Available and willing to participate for the duration of the study and follow-up visit.

7. Willing and able to comply with the protocol requirements, including the prohibitions and restrictions specified in Section 4.3.

8. Willing to provide verifiable identification.

9. Having a means to be contacted.

Contraceptive (birth control) use by women should be consistent with local regulations regarding the acceptable methods of birth control for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of birth control methods for participants in clinical studies.

4.2. Exclusion Criteria

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

1. Having received any candidate Ebola vaccine.
2. Diagnosed with EVD, or prior exposure to Ebola virus, including travel to an area with Ebola outbreak less than 1 month prior to screening (if applicable).
3. Having ever received any experimental candidate Ad26- or MVA-based vaccine in the past.
4. Known allergy or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine products (including any of the constituents of the study vaccines), including known allergy to chicken or egg protein and gentamicin.
5. Presence of acute illness (this does not include minor illnesses such as diarrhea or mild upper respiratory tract infection) or temperature ≥38.0ºC on Day 1. Participants with such symptoms will be excluded from enrollment at that time but may be rescheduled for enrollment at a later date.
6. HIV type 1 or type 2 infection, based on the medical history reported by the participant.
7. Criterion modified per Amendment 1

   7.1 Criterion modified per Amendment 2

   7.2 Pregnant, breast-feeding, or planning to become pregnant while enrolled in this study until at least 3 months post Dose 1 vaccination, 28 days post Dose 2vaccination, or 3 months post booster vaccination (Groups 5-6 only), whichever comes later.
8. Major surgery (per the investigator's judgment) within the 4 weeks prior to screening or planned major surgery during the study (from the start of screening onwards). Participants with planned surgical procedures to be conducted under local and loco-regional anesthesia may participate.
9. Post-organ and/or stem cell transplant whether or not with chronic immunosuppressive therapy.
10. Received any disallowed therapies as noted in Section 8 before the planned administration of Dose 1.
11. Received an investigational drug or investigational vaccine or used an invasive investigational medical device within 3 months prior to screening, or current or planned participation in another clinical study during the study.

    Note: Participation in an observational clinical study is allowed.

12. Criterion modified per Amendment 2

    12.1 Received or plans to receive:

    a. Licensed live-attenuated vaccines within 28 days before or after planned administration of the first or second study vaccine or booster dose (Groups 5-6 only);

    b. Other licensed (not live) vaccines within 14 days before or after planned administration of the first or second study vaccine or booster dose (Groups 5-6 only).

13. Donation of a unit of blood within 12 weeks before Day 1 or plans to donate blood during participation in the study (from the start of screening onwards).

14. Receipt of blood products within 4 months or immunoglobulins within 2 months prior to the planned administration of Dose 1 vaccination (Ad26.ZEBOV) and foreseen during participation in the study.

15. Current or past abuse of alcohol, recreational or narcotic drugs, which in the investigator's opinion would compromise the participant's safety and/or compliance with the study procedures.

16. Unable to communicate reliably with the investigator.

17. Unlikely to adhere to the requirements of the study in the opinion of the investigator.

18. Employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

19. Under legal guardianship or incapacitation.

20 History of an underlying clinically significant acute or chronic medical condition (eg, severe chronic obstructive pulmonary disease or clinically significant congestive heart failure, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, Alzheimer's disease, immune suppression, bleeding/clotting disorder, autoimmune disease, active malignancy, poorly controlled asthma, active tuberculosis, or other systemic infections) or physical examination findings for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

21 Criterion added per Amendment 2

Difficulty in taking blood samples.

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

4.3. Prohibitions and Restrictions

Potential participants must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Women of childbearing potential must remain on an acceptable effective method of birth control consistent with local regulations regarding the use of birth control methods for participants in clinical studies (see inclusion criteria in Section 4.1) until at least 3 months post Dose 1 vaccination or 28 days post Dose 2 vaccination or 3 months post booster vaccination (Groups 5-6 only), whichever comes later. If the social situation of a woman of childbearing potential changes (eg, woman who is not heterosexually active becomes active), she must begin a highly effective method of birth control, as described above in Section 4.1, until at least 3 months post Dose 1 vaccination or 28 days post Dose 2 vaccination or 3 months post booster vaccination (Groups 5-6 only), whichever comes later.

   Note: Prior to each study vaccine administration, a urine pregnancy test should be performed for women of childbearing potential.

2. In case of a new Ebola outbreak: participants should not travel to an area with Ebola outbreak while enrolled in the study from the start of screening onwards until the 21-day post Dose 2/booster dose (Groups 5-6 only) visit. If applicable, any traveling to an area with Ebola outbreak should be documented in the electronic case report form (eCRF).

3. Refer to Section 8 for details regarding prohibited and restricted therapy during the study.

4. Agree to follow all requirements that must be met during the study as noted in the inclusion and exclusion criteria (eg, contraceptive requirements).

5. STUDY VACCINE ALLOCATION AND BLINDING

Study Vaccine Allocation

Procedures for Randomization

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 4 vaccination groups for the main part of the study (Groups 1-4) and 1 of 2 groups for the Booster Cohort (Groups 5-6) based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks. The IWRS will assign a unique code, which will dictate the study vaccine assignment and matching study vaccine kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

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

Data that may potentially unblind the study vaccine allocation (ie, antibodies to study vaccine, study vaccine preparation/accountability data, or other specific laboratory data) will be handled with special care to ensure that the site and sponsor personnel involved in the review and determination of causality of serious adverse events reported during the study will remain blinded until final database lock. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding. The pharmacy and preparation of study vaccine will be monitored by an independent study vaccine monitor (see Section 17.8).

Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is locked. The investigator may in an emergency determine the identity of the study vaccine by contacting the IWRS. While the responsibility to break the code in emergency situations resides solely with the investigator, it is recommended that the investigator contacts the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is locked. However, for the primary analysis, the randomization codes and, if required, the translation of randomization codes into vaccination and control groups will be disclosed to authorized sponsor personnel involved in the analysis of the data. At the time of the primary analysis, the participants, the investigator(s) and study site personnel will remain blinded to individual participants' study vaccine allocation.

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

6. DOSAGE AND ADMINISTRATION

An overview of the study vaccination schedule is provided in Section 3.1, Table 1. All participants will receive a vaccination, according to randomization, on Day 1, on Day 57, and on Day 177 (Groups 5-6 only) at the following dose levels:

- Ad26.ZEBOV: $5x10^{10}$ vp, supplied in a single-use vial (0.5 mL extractable) (Groups 1, 2, 3, 5);
- MVA-BN-Filo: $1x10^{8}$ Inf U, supplied in a single-use vial (0.5 mL extractable) (Groups 1, 2, 3, 5);
- Placebo: 0.9% saline, 0.5 mL (Groups 4 and 6).

Blinding will be achieved by preparation of study vaccine by unblinded qualified study site personnel not involved in any other study-related procedure, and by the administration of study vaccine in a masked syringe by a blinded study vaccine administrator.

Ad26.ZEBOV and MVA-BN-Filo, or placebo, will be administered as 0.5-mL IM injections in the deltoid muscle. The injection site should be free from any injury, local skin condition, or other issue that might interfere with the evaluation of local reactions (eg, significant tattoo). In each participant, it is recommended that the second vaccination is administered in the opposite deltoid muscle from the first vaccination (unless the opposite arm has a condition that prevents evaluating the arm after injection) and it should be recorded in the eCRF in which arm the vaccination has been administered. The booster dose may be administered in either deltoid. No local or topical anesthetic will be used prior to the injection.

After each vaccination, participants will remain at the study site for at least 30 minutes for presence of any acute reactions and solicited events, or longer if deemed necessary by the investigator (eg, in case of grade 3 adverse events).

As with any vaccine, allergic reactions following vaccination with the study vaccine are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available and a medically qualified member of the study site personnel trained to recognize and treat anaphylaxis must be present at the study site during the entire vaccination procedure and postvaccination monitoring period.

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

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

6.1. Criteria for Postponement of Vaccination

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

- Acute illness at the time of vaccination (this does not include minor illnesses such as diarrhea or mild upper respiratory tract infection);
- Fever (body temperature ≥38.0°C) at the time of vaccination.

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

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

6.2. Contraindications to Second Vaccination

A participant will not be given the Dose 2 or booster dose vaccination if he or she experiences any of the following events at any time after the Dose 1 vaccination:

1. Anaphylaxis clearly attributable to vaccination with study vaccine; *OR*
2. Generalized urticaria within 72 hours of vaccination considered to be related to study vaccine; *OR*
3. A serious adverse event considered to be related to study vaccine; *OR*
4. Injection site ulceration, abscess, or necrosis considered to be related to study vaccine; *OR*
5. Any other safety concern threatening the participant's safety.

Participants experiencing any of the events described above must not receive any further study vaccine but should continue be monitored for safety and for immunogenicity according to the protocol if this does not result in safety risks for the participant.

7. STUDY VACCINE COMPLIANCE

Study vaccine will be administered as an IM injection by blinded qualified study site personnel at the study site. Details of each administration will be recorded in the eCRF (including date and time of injection and arm used for injection). For blinding procedures, see Section 5.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy-specific therapies such as analgesic/antipyretic medications, nonsteroidal anti-inflammatory drugs, vaccines, and immunomodulators/suppressors (eg, cancer chemotherapeutic agents, systemic corticosteroids) administered up to 30 days prior to the first dose of study vaccine and previous vaccinia/smallpox vaccination at any time prior to study entry must be recorded in the eCRF at screening.

Concomitant therapies such as analgesic/antipyretic medications, nonsteroidal anti-inflammatory drugs, vaccines, and immunomodulators/suppressors (eg, cancer chemotherapeutics, systemic corticosteroids) must be recorded from Dose 1 vaccination until 28 days post Dose 1 vaccination, from Dose 2 vaccination until 28 days post Dose 2 vaccination, and from the booster dose vaccination until 28 days post booster dose (Groups 5-6 only). All other concomitant therapies should also be recorded beyond these time frames until the end of the study if administered in conjunction with serious adverse events (refer to Section 12.3.2).

Use of any experimental medication (including experimental vaccines other than the study vaccine) within 3 months prior to screening and during the study is not allowed.

Information on concomitant use of herbal supplements or vitamins will not be collected.

All women of childbearing potential must use adequate birth control measures prior to randomization as described in Section 4.1.

Participants are allowed to receive all routine immunizations according to local schedules, taking into consideration the following restrictions. These routine immunizations should not be administered at least 14 days before (or at least 14 days after) administration of any study vaccine to avoid any potential interference in efficacy of the routine immunizations or the interpretation of immune responses to study vaccines, as well as to avoid potential confusion with regard to attribution of adverse events. Vaccination with licensed live-attenuated vaccines within 28 days before or after administration of a study vaccine is prohibited. However, if a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine.

Chronic or recurrent use of immunomodulators/suppressors, eg, cancer chemotherapeutic agents, systemic corticosteroids is prohibited during the study and within 30 days before the planned administration of the first dose of study vaccine. Note: Ocular, topical, or inhaled steroids are allowed.

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

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of all measurements and evaluations applicable to this study.

Visit windows are provided in the TIME AND EVENTS SCHEDULE. In case the Dose 2 or booster dose vaccination is postponed, the timing of the post Dose 2 and booster dose visits will be determined relative to the actual day of vaccination. The participant should be encouraged to come within these windows.

Additional urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during participation in the study.

The total blood volume to be collected from each participant in the immunogenicity subset will be approximately 25.5 mL. For the Booster Cohort, approximately 68 mL total blood volume will be collected (refer to Section 9.2).

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

9.1.2. Screening, Vaccination, Postvaccination Visits, and Follow-up

At baseline (Day 1, day of Dose 1 vaccination) and after signing and dating the ICF (see Section 16.2.3), screening assessments will be performed as indicated in the TIME AND EVENTS SCHEDULE. If needed, the screening activities may be split over multiple visits, with a maximum of up to 28 days between signing of the ICF and Dose 1 vaccination.

Only participants complying with the criteria specified in Section 4 will be included in the study.

The overall eligibility of the potential participant will be assessed once all required evaluations, including inclusion and exclusion criteria, are available. If rescreening is required, all screening procedures should be repeated. Study participants who qualify for inclusion will be enrolled and will receive Dose 1 vaccination on the same day.

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

Eligible participants will be allocated to a vaccination group as described in Section 5. Before each vaccination, a urine pregnancy test (only for women of childbearing potential), a full physical examination (before Dose 1, Day 1) or an abbreviated, symptom-directed physical examination (before Dose 2 and before the booster dose [Groups 5-6 only]), and measurement of vital signs will be performed as indicated by the investigator.

Participants will be vaccinated as described in Section 6. After each vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events, or longer if deemed necessary by the investigator (eg, in case of grade 3 adverse events). Solicited and unsolicited adverse events emerging during the observation period will be recorded in the eCRF.

Upon discharge from the study site, participants will receive a thermometer (to measure body temperature), a ruler (to measure local injection site reactions), and a participant diary to record body temperature and symptoms of solicited local (at injection site) and systemic adverse events and will be trained on how to collect this information. The participants will record symptoms of

solicited local and systemic adverse events in the diary in the evening after each vaccination and then daily for the next 7 days. The diary cards will be reviewed by study site personnel at the Day 57 visit (before Dose 2 vaccination), at the Day 78 visit, and at the Day 184 visit (Groups 5-6 only).

All adverse events and special reporting situations, whether serious or nonserious, that are related to study-related procedures or to non-investigational (concomitant) sponsor products, and pregnancy (if applicable), will be reported from the time a signed and dated ICF is obtained onwards.

Other serious adverse events and special reporting situations will be reported from first dose of study vaccine until the end of the study.

Other nonserious adverse events and special reporting situations (ie, not related to study-related procedures or non-investigational [concomitant] sponsor products) will be reported from first dose of study vaccine until 28 days after first dose of study vaccine, from the second dose of study vaccine until 28 days thereafter, and from the booster dose until 28 days thereafter (Groups 5-6 only). Participants will be asked about the occurrence of unsolicited adverse events at the Day 57 visit (before Dose 2 vaccination), at the Day 78 visit, at the Day 177, 184 and 198 visits (Group 5-6 only), and by means of a telephone call at Days 29 and 85, and at Day 205 (Groups 5-6 only).

Unsolicited adverse events with the onset date outside the time frame defined above (>28 days after previous study vaccination), which are ongoing on the day of the subsequent vaccination, should be recorded in the eCRF Adverse Event page.

Clinically relevant medical events occurring between signing of the ICF and first vaccination will be collected on the eCRF Medical History page as pre-existing conditions.

Participants will come to the study site 21 days post Dose 2 vaccination for safety and immunogenicity assessments. Participants in Groups 5 and 6 will also return to the site 7 and 21 days post booster dose vaccination for safety and immunogenicity assessments.

Participants in Groups 1-4 will be contacted via a telephone call 6 months post Dose 2 (ie, on Day 237 post Dose 1 vaccination) to assess safety. Participants in Groups 5-6 will not be contacted at that time but will return to the site 6 and 12 months post booster dose vaccination for long term immunogenicity follow-up.

Refer to Section 9.2 for details on the immunogenicity evaluations and Section 9.3 for the safety evaluations.

9.2. Immunogenicity Evaluations

Blood samples (8.5 mL) for humoral immunogenicity assessments (ie, analysis of antibodies binding to EBOV GP, using ELISA [EU/mL]) will be collected from participants in the immunogenicity subset and Groups 5-6 at the time points indicated in the TIME AND EVENTS SCHEDULE.

For Groups 5-6 only, an assessment of neutralizing antibodies against the Ad26 vector will be performed at baseline (pre Dose 1), pre booster vaccination (Day 177), and at 21 days post booster vaccination (Day 198).

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

The analysis of the immunogenicity samples will be done at a specialized laboratory.

9.3. Safety Evaluations

9.3.1. Safety Assessments

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

The sponsor has mechanisms, teams, and procedures in place to systematically analyze the safety profile of its investigational products during clinical development, including a multidisciplinary SMT dedicated to the Ebola vaccines development. SMTs are product-based, cross-functional collaborative teams responsible for review, assessment, and evaluation of medical safety data arising from any source throughout the Product Lifecycle. The SMT performs assessments in order to identify changes in safety profiles or potential safety signals. Based on these safety evaluations, the SMT will determine the appropriate safety-related actions to be taken with respect to the study vaccine based on its benefit-risk profile for participants in clinical studies, including VAC52150EBL3004.

Additionally, the following procedures will be in place to identify timely and assess in due time any relevant safety information (serious adverse events or a trend in unsolicited adverse events) which may emerge:

- An assessment (within 24 hours) by a blinded study physician of a serious adverse event reported by the study site (see Section 12.3.2 for more details).
- A medical evaluation of serious adverse events reported by a blinded study physician to detect timely any relevant trend in the safety data (number, severity, and seriousness of serious adverse events).
- An escalation of a suspected serious adverse event or a safety signal emerging to the SMT.

Any clinically relevant changes occurring during the study must be recorded in the eCRF Adverse Event page.

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

The study will include the following evaluations of safety and reactogenicity at the time points provided in the TIME AND EVENTS SCHEDULE:

Adverse Events

All adverse events will be reported as specified in Section 12.3.1.

Solicited Adverse Events

After each vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events, or longer if deemed necessary by the investigator. Upon discharge from the study site, participants will be provided with a diary and instructions on how to complete the diary: symptoms of solicited local and systemic adverse events will be collected in the diary in the evening after each vaccination and then daily for the next 7 days. The participants will complete their diary cards at home and these will be reviewed by study site personnel at the Day 57 visit (before Dose 2 vaccination) and at the Day 78 visit, and at the Day 184 visit (Groups 5-6 only). Diary information will be transcribed by the study personnel in the diary eCRF pages. Once a solicited symptom from a diary is considered to be of severity grade 1 or above, it will be referred to as a solicited adverse event.

Solicited Injection Site (Local) Adverse Events

Participants will be asked to note in the diary occurrences of pain/tenderness, erythema, induration/swelling, and pruritus at the study vaccine injection site daily for 7 days postvaccination (day of vaccination and the subsequent 7 days). The extent (largest diameter) of any erythema, and induration/swelling should be measured (using the ruler supplied) and recorded daily.

Solicited Systemic Adverse Events

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

Fever is defined as endogenous elevation of body temperature ≥38.0°C, as recorded in at least one measurement.[5]

Participants will also be instructed on how to note daily in the diary symptoms for 7 days postvaccination (day of vaccination and the subsequent 7 days) of the following events: fatigue, headache, nausea, myalgia, arthralgia, chills, and fever.

Physical Examination

A full physical examination (excluding genito-urinary system), including height and body weight, will be carried out at screening (Day 1). At other visits, an abbreviated, symptom-directed examination will be performed based on any clinically relevant issues, clinically relevant symptoms and medical history. The symptom-directed physical examination may be repeated if deemed necessary by the investigator. Physical examinations will be performed by the investigator or by a designated medically-trained clinician.

Vital Signs

Blood pressure, pulse/heart rate and oral body temperature will be assessed before each vaccination and at other visits as indicated in the TIME AND EVENTS SCHEDULE.

Blood pressure and pulse/heart rate measurements will be assessed in supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Supine blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

9.3.2. Study Vaccination Pausing Rules

The investigators and the sponsor's medical monitor will review the safety of enrolled participants on an ongoing basis and will halt vaccination of further participants in case any of the pre-specified pausing rules described in this section are met. The sponsor's medical monitor will be involved in all discussions and decisions.

The occurrence of any of the following events will lead to pause in further study vaccination.

1. Death of a participant, considered related to study vaccine or if the causal relationship to the study vaccine cannot be excluded; OR
2. One or more participants experience a life-threatening or serious adverse event (solicited or unsolicited) that is determined to be related to study vaccine; OR
3. One or more participants experience anaphylaxis or generalized urticaria within 24 hours of vaccination, clearly not attributable to other causes than vaccination with study vaccine.

All sites will be notified immediately in case of a study pause. The clinical sites will be allowed to resume activities upon receipt of a written notification from the sponsor. These communications will be forwarded by the investigator to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and by the sponsor to the relevant health authorities, according to local standards and regulations.

9.4. Sample Collection and Handling

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

Refer to the TIME AND EVENTS SCHEDULE for the timing and frequency of all sample collections.

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

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

10.1. Completion

A participant in Groups 1-4 will be considered to have completed the study if he or she has completed assessments at the Day 237 time point (ie, 6-months post Dose 2). A participant in Groups 5-6 will be considered to have completed the study if he or she has completed assessments at the Day 537 time point (ie, 12-months post booster dose).

10.2. Discontinuation of Study Vaccine/Withdrawal From the Study

Discontinuation of Study Vaccine

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

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

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

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

Participants meeting any of the reasons listed above must not receive any further study vaccine but should continue to be monitored for safety and immunogenicity according to the protocol if this does not result in safety risks for the participant. In case of early discontinuation of study vaccine due to an adverse event, the investigator will collect all information relevant to the adverse event

and safety of the participant, and will follow the participant to resolution, or until reaching a clinically stable endpoint.

Withdrawal From the Study

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

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

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

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

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study vaccine assigned to the withdrawn participant may not be assigned to another participant. Participants who withdraw will be replaced, as long as the participant has not been vaccinated yet.

If a participant withdraws early from the study, early withdrawal assessments should be obtained per the assessments for the 21-day post Dose 2 visit, with the exception of the immunogenicity assessments, if applicable. A participant who wishes to withdraw consent from participation in the study will be offered an optional visit for safety follow-up (before formal withdrawal of consent), but the participant has the right to refuse.

11. STATISTICAL METHODS

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

For the main part of the study (Groups 1-4), the primary safety and immunogenicity analyses will be conducted when all participants in Groups 1-4 have completed the 28-day post Dose 2 time point or discontinued earlier, and the database is locked. Only sponsor personnel not involved in the review and determination of causality of serious adverse events reported during the study will

be unblinded to Groups 1-4 at this time point. Investigator, study site personnel (except for those with primary responsibility for study vaccine preparation and dispensing), and participants will remain blinded to the study vaccine allocation until the last participant in Groups 1-4 completes the 6-month post Dose 2 time point (ie, Day 237, last study related visit) or discontinues earlier (and the database is locked). An interim analysis will be performed when all participants in Groups 1-4 have completed the 6-month post Dose 2 visit, ie, the last study-related visit (or discontinue earlier), and the database has been locked.

For the Booster Cohort (Groups 5-6), an interim analysis will be performed when all participants in Groups 5-6 have completed the 28-day post booster dose time point (or discontinued earlier). This analysis, based on the corresponding locked database, will include all available data (including safety and 21-day post booster dose immunogenicity data) up to the cut off. Only sponsor personnel not involved in the review and determination of causality of serious adverse events reported during the study will be unblinded to Groups 5-6 at this time point. Investigators, study site personnel (except for those with primary responsibility for study vaccine preparation and dispensing), and participants will remain blinded to the study vaccine allocation until the database is locked for the final analysis.

The final analysis will be conducted when all participants in the study have completed the last study-related visit or have discontinued earlier.

A planned analysis may be combined with the subsequent analysis, if deemed necessary (eg, when the dates of 2 planned database locks are very close).

11.1. Analysis Sets

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

Per Protocol Analysis Set: The per protocol analysis set will include all randomized and vaccinated participants, who received both Dose 1 and Dose 2 vaccinations (administered within the protocol-defined window), had at least one postvaccination (ie, after the date of vaccination) evaluable immunogenicity sample, and had no major protocol deviations that may influence the immune response. The per protocol analysis set will be defined for participants included in the immunogenicity subset. Similarly, the per protocol analysis set for the Booster Cohort (Groups 5-6) will include all vaccinated participants, who received Dose 1, Dose 2, and the booster vaccination (ie, both Dose 2 and Ad26.ZEBOV booster vaccination within the protocol-defined window), had at least one postvaccination (ie, after the date of vaccination) evaluable immunogenicity sample, and had no major protocol deviations that may influence the immune response.

11.2. Sample Size Determination

The following assumptions are used in the sample size determination:

- A standard deviation of 0.55 on the $\log_{10}$ scale (binding antibody levels against the EBOV GP using ELISA [EU/mL] 21 days post Dose 2 vaccination, following Dose 1 on Day 1 and Dose 2 on Day 57). This standard deviation is obtained by adding 10% to the maximum observed standard deviation at 56 days post Dose 1 vaccination in the Phase 2/3 studies and will also ensure adequate power in demonstrating lot-to-lot consistency at 56 days post Dose 1 vaccination (ie, secondary objective).
- An overall 5% dropout rate.

In addition, specific assumptions are made for the equivalence testing for the primary and secondary objective:

Assumptions specific to equivalence testing:

- A relative difference of 10% in GMC of binding antibodies between groups (ie, Groups 1 to 3). This is expressed as $GMC_{(1)} = 0.9 \times GMC_{(3)}$, where $GMC_{(1)}$, $GMC_{(2)}$, and $GMC_{(3)}$ denote the ordered GMC. This relative difference is based on both the process variability in vp content of the Ad26.ZEBOV lots and Inf U content of MVA-BN-Filo lots. A linear relationship between $\log_{10}$-transformed vaccine contents (ie, Ad26.ZEBOV and MVA-BN-Filo) and $\log_{10}$-transformed GMC of binding antibodies (ELISA GMC) was assumed.
- Clinical equivalence limits on the GMC ratio are 0.5 and 2.0.

Under the above assumptions, a total of 144 participants per group receiving Ad26.ZEBOV as Dose 1 and MVA-BN-Filo as Dose 2, would yield an overall power of at least 90% to show immunogenic equivalence of the 3 groups (Groups 1 to 3) 21 days post Dose 2 vaccination (ie, with 96.55% power for each of the 3 pairwise comparisons [ie, Groups 1 vs 2, 1 vs 3 and 2 vs 3]). PASS 11 is used for the sample calculations. In order to enlarge the safety database, the total number per group was increased to 234 (ie, additional 90 participants per group for safety only).

A randomization ratio of 6:6:6:1 (Group 1:Group 2:Group 3:Group 4) yields an overall sample size of 741 participants, with 234 participants per group (in Groups 1 to 3) receiving Ad26.ZEBOV and MVA-BN-Filo, and 39 participants receiving placebo (Group 4).

Due to the recent (on 11-March-2020) WHO declared COVID-19 pandemic, a potential higher dropout rate (ie, higher than 5%) may occur. In addition, some participants in the immunogenicity subset may be excluded from primary immunogenicity equivalence testing because of:

- Participant not receiving Dose 2; *OR*
- Participant receiving Dose 2 outside the protocol defined window; *OR*
- Participant not attending the 21-day post Dose 2 visit; *OR*
- Participant attending the 21-day post Dose 2 visit outside the protocol-defined window.

To mitigate these issues, additional participants may be recruited in the immunogenicity subset.

Shortly after participants received Dose 1 vaccination, 'stay-at-home' orders were imposed in the areas where the sites were located and approximately 22% of participants did not return to the site within the protocol defined windows (±3 days) for Dose 2 administration.

Examination of the immunogenicity data from studies (VAC52150EBL2001 and VAC52150EBL2002) in which Dose 2 was administered at intervals ≥56 days reveals that although there appears to be trend of increasing GMCs with increasing intervals between Dose 1 and Dose 2, the variability (standard deviation) of the immune responses (binding antibody levels against the EBOV GP using ELISA [EU/mL]) remains stable and in line with the currently assumed standard deviation of 0.55 (on the $\log_{10}$-scale). Assuming that the delayed Dose 2 administration will be randomly distributed among the groups (ie, Groups 1-4), widening the acceptable time frame to administer Dose 2 by increasing the upper limit of the window to 28 days (ie, Day 57+28 days) is not expected to adversely affect the primary and secondary objectives of the study. With the widened window, the number of additional participants necessary to maintain approximately 90% power to test the primary and secondary hypotheses will be reduced.

Approximately 60 participants will be randomized in a 5:1 active:placebo ratio (Group 5:Group 6), which will provide a reasonable estimation of the humoral immune response to a booster dose.

11.3. Immunogenicity Analyses

Descriptive statistics (including geometric means with their corresponding 95% CIs, median, interquartile range, minimum, maximum, as applicable) will be calculated for continuous immunologic parameters at each time point. Graphical representations of immunologic parameters will be prepared, as applicable. Frequency tabulations will be calculated for discrete (qualitative) immunologic parameters at each time point.

To assess the primary objective, each pairwise comparison (ie, Groups 1 vs 2, 1 vs 3, 2 vs 3) of the anti-EBOV GP binding antibody responses 21 days post Dose 2 vaccination with MVA-BN-Filo will be based on ratios of the GMC with corresponding 95% CI. Equivalence of any 2 groups will be shown if the 95% CI of the estimated GMC ratio lies entirely within 0.5 and 2.0. Lot-to-lot consistency is accomplished if equivalence is shown for all 3 pairwise comparisons.

For the secondary objective, each pairwise comparison of the anti-EBOV GP binding antibody responses 56 days post Dose 1 vaccination with Ad26.ZEBOV will be based on ratios of the GMCs with corresponding 95% CI. Equivalence of any 2 groups will be shown if the 95% CI of the estimated GMC ratio lies entirely within 0.5 and 2.0. Lot-to-lot consistency (for Ad26.ZEBOV) is accomplished if equivalence is shown for all 3 pairwise comparisons.

As a sensitivity analyses, both the primary and secondary hypotheses of equivalence will also be tested based on data of participants who received the second vaccination within the original window (±3 days) around the Day 57 visit.

11.4. Safety Analysis

No formal statistical testing of safety data is planned. All the participants who received at least 1 dose of the study vaccine will be included in the full analysis set. The reporting of the categorical safety data will include the incidence, severity, relatedness, and type of adverse events. Continuous safety parameters will be analyzed descriptively (showing the mean, standard deviation, median, and quartiles [Q1 and Q3]).

Baseline for all vital signs and physical examinations will be defined as the last evaluation done before Dose 1 vaccination.

Adverse Events (Including Reactogenicity)

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For each adverse event, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by group. In addition, comparisons between groups will be provided if appropriate. All reported adverse events and events-related diary information (solicited local at injection site and systemic, and unsolicited) with onset within 28 days post Dose 1, Dose 2 or booster dose vaccination (ie, treatment-emergent adverse events) will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by vaccination group.

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

Solicited local (at injection site) and systemic adverse events will be summarized descriptively. The overall frequencies per vaccine group as well as frequencies according to severity and duration will be calculated for solicited adverse events. In addition, the number and percentages of participants with at least one solicited local (at injection site) or systemic adverse event will be presented. Frequencies of unsolicited adverse events, separately for all and vaccination-related only, will be presented by System Organ Class and preferred term, while those of solicited adverse events will be presented only by preferred term.

Vital Signs

Descriptive statistics of blood pressure (systolic and diastolic; supine), pulse/heart rate, and oral temperature will be summarized. The percentage of participants with values beyond clinically important limits will be summarized.

Physical Examination

Physical examination findings will be listed.

12. ADVERSE EVENT REPORTING

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

Method of Detecting Adverse Events and Serious Adverse Events

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

Solicited Adverse Events

Solicited adverse events are predefined local (at the injection site) and systemic events for which the participant is specifically questioned and which are noted by participants in their diary (see Section 9.1.2).

Unsolicited Adverse Events

Unsolicited adverse events are all adverse events for which the participant is not specifically questioned in the participant diary (see Section 9.1.2).

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the study vaccine. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH])

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

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

Serious Adverse Event

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

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

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

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study vaccine and the event (eg, death from anaphylaxis), the event must be reported as a 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 Ad26.ZEBOV, MVA-BN-Filo, the expectedness of an adverse event will be determined by whether or not it is listed in the IB.

Adverse Event Associated With the Use of the Study Vaccine

An adverse event is considered associated with the use of the study vaccine if the attribution is related 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 diseases, concomitant therapies). This applies to all adverse events, whether serious or nonserious.

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

Related: there is a reasonable possibility that the study vaccine contributed to the adverse event.

Unrelated: there is no suspicion that there is a relationship between the study vaccine and the adverse event; there are other more likely causes and administration of the study vaccine is not suspected to have contributed to the adverse event.

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

12.1.3. Severity Criteria

All adverse events will be coded for severity using the toxicity grading tables in Attachment 1. For adverse events not identified in the table, the following guidelines will apply:

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

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

12.2. Special Reporting Situations

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

- Overdose of a sponsor study vaccine
- Accidental or occupational exposure to a sponsor study vaccine
- Medication error involving a sponsor product (with or without participant exposure to the sponsor study vaccine, eg, name confusion)
- Suspected abuse/misuse of a sponsor study vaccine
- Exposure to a sponsor study vaccine from breast-feeding

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

12.3. Procedures

12.3.1. All Adverse Events

Solicited adverse events will be recorded in a diary for each vaccination from the moment of vaccination until 7 days post each vaccination.

All adverse events and special reporting situations, whether serious or nonserious, that are related to study-related procedures or to non-investigational (concomitant) sponsor products, and pregnancy (if applicable), will be reported from the time a signed and dated ICF is obtained onwards.

Other serious adverse events and special reporting situations will be reported from first dose of study vaccine until the end of the study.

Other nonserious adverse events and special reporting situations will be reported from first dose of study vaccine until 28 days after first dose of study vaccine, from the second dose of study vaccine until 28 days thereafter, and from the booster dose until 28 days thereafter (Groups 5-6 only).

Unsolicited adverse events with the onset date outside the time frame defined above (>28 days after previous study vaccination), which are ongoing on the day of the subsequent vaccination, should be recorded on the eCRF Adverse Event page.

Clinically relevant medical events occurring between signing of ICF and first vaccination will be collected on the eCRF Medical History page as pre-existing conditions.

The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

The investigator will monitor and analyze the study data including all adverse event data as they become available and will make determinations regarding the severity of the adverse experiences and their relation to study vaccine. All adverse events will be deemed related to study vaccine or unrelated to study vaccine, according to Section 12.1.2.

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

All adverse events, regardless of seriousness, severity, or presumed relationship to study vaccine, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report all SUSARs to the investigator (and the head of the investigational institute where required). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and

documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

Participants will be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

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

12.3.2. Serious Adverse Events

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

Information regarding serious adverse events will be transmitted to the sponsor using the serious adverse event form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted electronically or 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 participant'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 vaccine or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs

during the course of a participant'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 eCRF). Note: Hospitalizations that were planned between signing of the ICF and first vaccination, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

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

12.3.3. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the serious adverse event form. Any participant who becomes pregnant during the study must be promptly withdrawn from further study vaccination but should continue participation in the study for follow-up of safety and immunogenicity if this does not result in a safety risk for the participant.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY VACCINE INFORMATION

14.1. Physical Description of Study Vaccines

14.1.1. Ad26.ZEBOV

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

The Ad26.ZEBOV vaccine will be supplied at a nominal concentration of $1x10^{11}$ vp/mL in 1-mL single-use glass vials as a frozen liquid suspension to be thawed before use. Each vial contains an extractable volume of 0.5 mL. Refer to the IB for a list of excipients.[3]

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

14.1.2. MVA-BN-Filo

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

The MVA-BN-Filo vaccine is supplied at a nominal concentration of $2x10^{8}$ Inf U/mL in 1-mL single-use glass vials as a frozen liquid suspension to be thawed before use. Each vial contains an extractable volume of 0.5 mL. Refer to the IB for a list of excipients.[4]

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

14.2. Packaging

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

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

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

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

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

A pharmacist/qualified staff member will prepare all doses for vaccine administration and provide it for dispensing. Blinding will be achieved by preparation of study vaccine by unblinded qualified study site personnel not involved in any other study-related procedures, and by the administration of study vaccine in a masked syringe by a blinded study vaccine administrator.

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

14.5. Study Vaccine Accountability

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

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

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

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

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Study protocol and IB and Addendum for Ad26.ZEBOV and MVA- BN-Filo
- Site Investigational Product Procedures Manual, Site Blinding Plan
- Syringes, needles, and study vaccines
- Laboratory manual, laboratory kits, requisition forms, and shipment boxes
- IWRS Manual
- Electronic Data Capture (eDC) Manual/eCRF Completion Guidelines
- Sample ICF
- Participant diaries
- Rulers, thermometers
- Participant wallet card

16. ETHICAL ASPECTS

16.1. Study-specific Design Considerations

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

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

The total blood volume to be collected is considered to be well below the limits of standard blood donation.

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 participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of participants 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 participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- 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 participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant 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 participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants

- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study vaccine
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the study 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 participants, 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

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

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants 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 they will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the

confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, if needed.

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

If the participant 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 participant or legally acceptable representative is obtained.

16.2.4. Privacy of Personal Data

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

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

The informed consent obtained from the participant 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 participant 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.

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

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

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand Ad26.ZEBOV, MVA-BN-Filo, to understand EVD, to understand differential vaccine responders, and to develop tests/assays related to Ad26.ZEBOV, MVA-BN-Filo, and EVD. The research may begin at any time during the study or the post-study storage period.

Each participant will be asked to consent voluntarily for their blood samples to be stored for other research studies that may be done after this study is completed. Participants unwilling to have their blood samples stored for future use, can participate in the immunogenicity assessments without having their blood samples stored for future testing. In such case, their blood samples will be destroyed after all the immunogenicity tests have been concluded (as agreed by the sponsor).

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

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research.

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 participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF 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 vaccine 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, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

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

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)

17.3. Participant Identification, Enrollment, and Screening Logs

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

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

The investigator must also complete a participant screening log, which reports on all participants who were seen to determine eligibility for inclusion in the 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: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; study vaccine receipt/dispensing/return records; study vaccine administration information; and date of study completion and reason for early discontinuation of study vaccine or withdrawal from the study, if applicable.

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

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

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

- Race
- HIV status, as reported by the participant
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination

The participant diary will be considered a source document. Information from the diary provided to participants to record symptoms of solicited local and systemic adverse events until 7 days post Dose 1, post Dose 2, and post booster dose (Groups 5-6 only) vaccinations, will be reviewed by the investigator or clinical designee to transcribe into the relevant parts of the eCRF as described in the CRF Completion Guidelines.

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

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All eCRF 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 eCRF are accurate and correct.

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

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

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

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

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

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. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study site personnel before the start of the study. The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

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

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 as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (vaccination unit and/or clinic records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF 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.

There will be independent monitoring of the pharmacy and preparation of study vaccine by an unblinded monitor (independent study vaccine monitor, see DEFINITIONS OF TERMS); regular monitors will be blinded.

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

Central monitoring will take place for data identified by the sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last visit for the last participant participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit/phone call 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 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 participants by the investigator
- Discontinuation of further study vaccine development

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

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

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

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be

published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

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

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3. Investigator's Brochure: JNJ-61210474 (Ad26.ZEBOV) Edition 6. Janssen Vaccines & Prevention B.V. (January 2019). For updated information, refer to Edition 6 Addendum 1 (Janssen Vaccines & Prevention, 17 May 2019).
4. Investigator's Brochure: JNJ-63839880 (MVA-BN-Filo [MVA-mBN226B]) Edition 12. Janssen Vaccines & Prevention B.V. (December 2018). For updated information, refer to Edition 12 Addendum 1 (Janssen Vaccines & Prevention, 17 May 2019).
5. Marcy SM, Kohl KS, Dagan R, et al./The Brighton Collaboration Fever Working Group. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine. 2004:22;551-556.
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ATTACHMENTS

Attachment 1: Toxicity Tables for Use in Studies Enrolling Healthy Adults

The abbreviations used in the following tables are:

FEV_1: forced expiratory volume in 1 second; IV: intravenous; Rx: therapy

CLINICAL ADVERSE EVENTS

Grading scale used for clinical adverse events is adapted from the Division of Microbiology and Infectious Diseases (DMID) Toxicity Tables (2007). For adverse events not included in the tables below, refer to the severity criteria guidelines in Section 12.1.3.

Cardiovascular	**Grade 1**	**Grade 2**	**Grade 3**
Arrhythmia		Asymptomatic, transient signs, no Rx required	Recurrent/persistent; symptomatic Rx required
Hemorrhage, blood loss	Estimated blood loss ≤100 mL	Estimated blood loss >100 mL, no transfusion required	Transfusion required
Respiratory	**Grade 1**	**Grade 2**	**Grade 3**
Cough	Transient; no treatment	Persistent cough	Interferes with daily activities
Bronchospasm, acute	Transient; no treatment; FEV_1 71%-80% of peak flow	Requires treatment; normalizes with bronchodilator; FEV_1 60%-70% (of peak flow)	No normalization with bronchodilator; FEV_1 <60% of peak flow
Dyspnea	Does not interfere with usual and social activities	Interferes with usual and social activities, no treatment	Prevents daily and usual social activity or requires treatment
Gastrointestinal	**Grade 1**	**Grade 2**	**Grade 3**
Nausea/vomiting	Minimal symptoms; caused minimal or no interference with work, school or self-care activities	Notable symptoms; required modification in activity or use of medications; did not result in loss of work or cancellation of social activities	Incapacitating symptoms; required bed rest and/or resulted in loss of work or cancellation of social activities
Diarrhea	2-3 loose or watery stools or <400 g/24 hours	4-5 loose or watery stools or 400-800 g/24 hours	6 or more loose or watery stools or >800 g/24 hours or requires IV hydration

Reactogenicity	Grade 1	Grade 2	Grade 3
Local reactions			
Pain/tenderness at injection site	Aware of symptoms but easily tolerated; does not interfere with activity; discomfort only to touch	Notable symptoms; required modification in activity or use of medications; discomfort with movement	Incapacitating symptoms; inability to do work or usual activities; significant discomfort at rest
Erythema/redness [a]	2.5-5 cm	5.1-10 cm	>10 cm
Induration/swelling [b]	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity
Itching at the injection site	Minimal symptoms; caused minimal or no interference with work, school, or self-care activities	Notable symptoms; required modification in activity or use of medications; did not result in loss of work or cancellation of social activities	Incapacitating symptoms; required bed rest and/or resulted in loss of work or cancellation of social activities
Systemic reactions			
Allergic reaction	Pruritus without rash	Localized urticaria	Generalized urticaria; angioedema or anaphylaxis
Headache	Minimal symptoms; caused minimal or no interference with work, school or self-care activities	Notable symptoms; required modification in activity or use of medications; did not result in loss of work or cancellation of social activities	Incapacitating symptoms; required bed rest and/or resulted in loss of work or cancellation of social activities
Fatigue/malaise	Minimal symptoms; caused minimal or no interference with work, school or self-care activities	Notable symptoms; required modification in activity or use of medications; did not result in loss of work or cancellation of social activities	Incapacitating symptoms; required bed rest and/or resulted in loss of work or cancellation of social activities
Myalgia	Minimal symptoms; caused minimal or no interference with work, school or self-care activities	Notable symptoms; required modification in activity or use of medications; did not result in loss of work or cancellation of social activities	Incapacitating symptoms; required bed rest and/or resulted in loss of work or cancellation of social activities

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Reactogenicity (continued)	Grade 1	Grade 2	Grade 3
Arthralgia	Minimal symptoms; caused minimal or no interference with work, school or self-care activities	Notable symptoms; required modification in activity or use of medications; did not result in loss of work or cancellation of social activities	Incapacitating symptoms; required bed rest and/or resulted in loss of work or cancellation of social activities
Chills	Minimal symptoms; caused minimal or no interference with work, school or self-care activities	Notable symptoms; required modification in activity or use of medications; did not result in loss of work or cancellation of social activities	Incapacitating symptoms; required bed rest and/or resulted in loss of work or cancellation of social activities

VITAL SIGNS TOXICITY GRADING

Grading scale used for vital signs is according to DMID Toxicity Tables (2007)

Vital Signs	LO/HI/N [a]	Mild (Grade 1) [b]	Moderate (Grade 2)	Severe (Grade 3)
Fever (°C)[c]	HI	38.0-38.4	38.5-38.9	>38.9
Fever (°F)	HI	100.4-101.1	101.2-102.0	>102.0
Tachycardia	HI	101-115 bpm	116-130 bpm	>130 bpm or ventricular dysrhythmias
Bradycardia	LO	50-54 or 45-50 bpm if baseline <60 bpm	45-49 or 40-44 bpm if baseline <60 bpm	<45 or <40 bpm if baseline <60 bpm
Hypertension (systolic) - mm Hg [d]	HI	141-150	151-160	>160
Hypertension (diastolic) - mm Hg	HI	91-95	96-100	>100
Hypotension (systolic) - mm Hg	LO	85-89	80-84	<80
Tachypnea - breaths per minute	HI	23-25	26-30	>30

[a] Low, High, Not Graded.
[b] If initial bound of grade 1 has gap from reference range or eligibility range, calculations based on the New England Journal of Medicine (NEJM) reference ranges.
[c] Oral temperature.
[d] Assuming participant is awake, resting, and supine; for adverse events, 3 measurements on the same arm with concordant results.

INVESTIGATOR AGREEMENT

VAC52150 (Ad26.ZEBOV, MVA-BN-Filo [mBN226B])
Clinical Protocol VAC52150EBL3004 Amendment 3

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: PPD Janssen Vaccines & Prevention B.V.

Signature: PPD Date: PPD

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.

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Approved, Date: 15 June 2020