Janssen Vaccines & Prevention B.V.*

Statistical Analysis Plan
(Interim and Final Analyses)
Amendment 3

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

Protocol VAC52150EBL2005; Phase 2

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

*Janssen Vaccines & Prevention B.V. is a Janssen pharmaceutical company of Johnson & Johnson and is hereafter referred to as the sponsor of the study.

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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AMENDMENT HISTORY

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	28 August 2019		Initial release
2	24 February 2020		Amendment 1
3	23 November 2020		Amendment 2
4	25 October 2021		Amendment 3

The overall rationale for Amendment 1: The purpose for this amendment is to align with the clinical trial protocol.

The changes made to the Statistical Analysis Plan (SAP) of VAC52150EBL2005, 28 August 2019, are listed below, including the rationale for each change and a list of all applicable sections.

Rationale: The laboratory samples and vital signs are only collected at screening and pre-dose 2. This means tabulations of abnormalities following the vaccination will not be done.

Section 5.2 Laboratory, Vital Signs and Physical Examinations

Rationale: The summary of the percentile for length is a less useful clinical parameter for children less than 24 months and will not be done.

Amendment 2
The overall reason for the amendment: The overall reason for the amendment is to ensure that final analysis Clinical Study Report (CSR) is completed within 6 months of study completion, in line with European Medicines Agency (EMA) Article 46.
The changes made to the SAP of VAC52150EBL2005 are listed below, including the rationale of each change and a list of all applicable sections.

Rationale: In order to expedite the final analysis, the interim analysis is being removed from the protocol. The final analysis will be performed at study end, now defined as database lock. This will occur after the last visit of the last participant in the study.

Section 1 Introduction
The text on interim analysis has been deleted.

Section 3 Interim Analysis and Data Monitoring Committee review
The text on interim analysis has been deleted.

Amendment 3 (This document)
The overall reason for the amendment: The current protocol Amendment 4 describes the extension of the study for participants originally enrolled in the control arm who consent to receiving the Ebola vaccine regimen. The extension phase will consist of a screening, vaccination and safety follow-up phase until 28 days post-dose 2. The primary interim analysis will be done when all participants have completed the 12 months post-dose-1 visit or left the study (ie,

completion of the main study), and the clinical database is locked and unblinded. This analysis will include all available data up to the 12 months post-dose-1 (D365) visit. Subsequently, participants in the control group who have not withdrawn during the main study, will be offered the Ebola vaccine regimen in an optional extension phase of the study.
his SAP is amended for describing the safety analyses on data of the extension phase, as well as re-introduction of the interim analyses, comprising all outputs on the main study part.

Rationale: In the extension phase, all participants of the control arm who completed the main study are offered the Ebola vaccination regimen. These participants will be followed up for safety data assessment.

Section 1 Introduction
The text on interim analysis has been added, as well as the safety analyses on extension phase data.

Section 1.6 Changes to planned analyses
The main study analyses are now considered as an interim analysis. The addition of the extension phase safety assessment with a repeat of the main study analyses are performed at final DBL.

Section 2.1 Analysis periods/phases
2.1.2 is added with the periods for the extension phase. This is identical to the main study periods, except for a follow-up period of 28 days.

Section 3 Interim Analysis and Data Monitoring Committee review
The main study analyses are considered the interim analyses.

Section 5.1.1 Definitions
AEs (unsolicited and solicited) will be summarized for the main study and extension phase separately. The listing of AEs of both phases are combined in the same listing, showing an extra column stating main study/extension phase.

ABBREVIATIONS

Ad26	Adenovirus serotype 26
AE	adverse event
CDC	Center for Disease Control and Prevention
CI	confidence interval
CRF	case report form
CTP	clinical trial protocol
IDMC	Independent Data Monitoring Committee
EBOV	Ebola virus
ECG	Electrocardiogram
eCRF	electronic case report form
ELISA	Enzyme-linked immunosorbent assay
EU	ELISA units
GMC	Geometric mean antibody concentration
FA	Full Analysis Set
FDA	Food and Drug Administration
GP	glycoprotein
IWRS	interactive web response system
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per Protocol
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
VNA	Virus neutralization assay
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes both the interim and final analyses of the VAC52150EBL2005 study. The interim analysis will be performed when last participant has completed the 12 months post-dose-1 visit or has left the main study (ie, completion of the main study) and the interim database is locked and unblinded. Subsequently, participants who were originally randomized to the control arm and who have not withdrawn during the main study, will be offered the Ebola vaccine regimen in an optional extension phase of the study. The final analysis will then be performed when all participants have completed the last study-related visit or discontinued earlier (ie, when the last participant in the extension phase has completed the last study visit or left the study).

1.1. Trial Objectives

The objectives of the study and corresponding endpoints are as shown in Table 1. For further details, see the clinical trial protocol (CTP)[1]

Main study

Table 1: Study objectives and endpoints

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

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

Extension Phase

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

1.2. Trial Design

1.2.1. Main Phase

Study VAC52150EBL2005 is a Phase 2, randomized, active-controlled, double-blind study to evaluate the safety, reactogenicity, and immunogenicity of Ad26.ZEBOV (Dose 1) at a dose of $5x10^{10}$ viral particles (vp) followed by MVA-BN-Filo (Dose 2) at a dose of $1x10^{8}$ infectious units (Inf U) administered 56 days later in healthy infants aged 4-11 months (ie, ≥4 months up to <12 months) in Guinea and Sierra Leone. A total of 107 infants is planned to be enrolled and randomized to study vaccine (Ad26.ZEBOV, MVA-BN-Filo) or active control (MenACWY, MenACWY) in a blinded fashion. Approximately equal numbers of participants will be enrolled in each country. Within each country, there will be stratification by age group (ie, ≥4 to ≤8 months, and >8 to <12 months of age). Enrollment of participants will start with vaccination of a sentinel cohort of 16 infants before exposing the remainder of the infants to the study intervention (see Section 3.1 of the CTP[1] for further details).

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

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

Participants in the control arm will receive the World Health Organization (WHO)-prequalified MenACWY as Dose 1 on Day 1, and as Dose 2 on Day 57. The MenACWY vaccine will be administered as a 0.5-mL IM injection into the anterolateral thigh. In keeping with the recommended immunization regimen for MenACWY, all participants (including those randomized to Ad26.ZEBOV, MVA-BN-Filo arm) will receive a dose of MenACWY at the

6-month post-dose 2 visit. An overview of the study vaccination schedule is shown in Table 2. For further details, see Sections 2 and 6 of the CTP[1].

Table 2: Study Vaccination Schedule

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

1.2.2. Extension Phase

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

1.3. Statistical Hypotheses for Trial Objectives

No formal statistical hypothesis testing is planned.

1.4. Sample Size Justification

The sample size is not based on formal hypothesis testing considerations. Active control recipients are included for blinding purposes and safety analyses and will provide control specimens for immunologic assays. The overall planned size of 107 participants expands the safety and immunogenicity database for VAC52150 to infants. See Section 11.2 of the CTP[1] for details on the sample size justification.

1.5. Randomization and Blinding

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention arms based on a computer-generated randomization schedule prepared before the start of the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by country and age group. The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. A sentinel cohort of 16 participants will be randomized in a 1:1 ratio to receive study vaccine (Ad26.ZEBOV, MVA-BN-Filo) or active control (MenACWY, MenACWY). An independent data monitoring committee (IDMC) which is instituted before study start will review data of the sentinel participants and give recommendations with regard to exposing the remainder of the participants to the study vaccine. Upon completion of the sentinel cohort and favorable IDMC recommendation, the remainder of the participants will be randomly assigned to study vaccine or active control in a 5:2 ratio (see Section 3.1 of the CTP[1]).

Data that may potentially unblind the intervention assignment (ie, study intervention preparation/ accountability data, or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding. The pharmacy and preparation of study intervention will be monitored by an independent study intervention monitor (see Section 17.8 of the CTP[1] for further details).

1.6. Changes to Planned Analyses

Since laboratory samples are only collected at screening and pre-dose 2 timepoints, and vital signs are only measured at screening and pre-dose, no summary tables per time point will be created even though the analyses were planned in the protocol.

Since the percentile for length is a less useful clinical parameter for children less than 24 months, the analysis of the percentile for length will not be done.

2. GENERAL ANALYSIS DEFINITIONS

All types of analysis together with the description of rules for handling missing or incomplete data are described later in this document. These analyses will include vaccinated participants with respect to the actual vaccine administered (ie, Ad26.ZEBOV as Dose 1 followed by MVA-BN-Filo as Dose 2 or MenACWY as Dose 1 followed by another MenACWY as Dose 2). Also, participants who receive only the first vaccination (Ad26.ZEBOV or MenACWY) will be included in accordance with the intervention arm with that first vaccination. Otherwise, the participant will be excluded from summary tables and graphs but will be included in listings. For instance, a participant who will receive MVA-BN-Filo as Dose 1 will not be included in summary tables and graphs.

In general, the study data will be analyzed as follows:

- Categorical variables will be summarized with a frequency table presenting counts and percentages.
- Continuous variables will be summarized using the following statistics, as appropriate: number of observations, arithmetic mean, geometric mean, corresponding 95% CI, standard deviation, standard error, median, quartiles (Q1 and Q3), minimum and maximum.

Baseline value will be defined as the value of the last available assessment performed prior to the first vaccination (Dose 1) on Day 1, unless specified otherwise.

For safety assessments, the *baseline value* will be an assessment performed prior or on the date (if only time of assessment is missing) of the first vaccination. The baseline value for immunogenicity assessments will be an assessment performed before or on the date of the first vaccination. In case of multiple values, the value closest to the vaccination will be used as the baseline.

V*isit day* will be determined relative to the actual day of vaccination (ie, date of Dose 1 or Dose 2).

2.1. Analysis Periods/Phases

Because the analysis of adverse events (AEs) will be presented per period (and not per time point), these will be assigned to the analysis periods based on Table 3 for the main study, and on Table 4 for the extension phase.

For the analysis that will be presented by time point (e.g. immunogenicity data), the electronic case report form (eCRF) visit schedules will be used for the post baseline assessments as follows:

- For the analysis based on the per protocol set, only assessments that fall within the protocol defined visit window will be used.
- For other analyses based on the full analysis set (if applicable), the assessments that fall outside the protocol defined windows will also be included. If only unscheduled visits are present for a time point, then the one closest to the scheduled visit will be used. If distances of multiple assessments to the scheduled visit are equal, the measurement with the latest date will be used.

Table 3: Analysis Period Definitions (Main Study)

Phase	Period	Interval	
		From	To
Screening		Date and time of signing the informed consent form	One minute prior to start of post dose 1 period
Regimen	Post-dose 1	Date and time of first vaccination	Minimum of: a) 23:59 on the date of last contact (for early discontinuation) b) 23:59 on the date of database cut-off date in case of interim c) 23:59 of 28 days after the first vaccination (23:59 of day of vaccination + 28 days) d) One minute prior to post-dose 2 period
Follow-up 1		One minute after post-dose 1 period ends	Minimum of: a) 23:59 on the date of last contact (for early discontinuation) b) 23:59 on the date of database cut-off date in case of interim c) One minute prior to post-dose 2 period
Regimen	Post-dose 2	Date and time of second vaccination	Minimum of: a) 23:59 on the date of last contact (for early discontinuation) b) 23:59 on the date of database cut-off in case of interim analysis c) 23:59 of 28 days after the second vaccination (23:59 of day of vaccination + 28 days)
Follow-up 2		One minute after post-dose 2 period ends	Minimum of: a) 23:59 on the date of last contact (for early discontinuation) b) 23:59 on the date of database cut-off in case of interim analysis c) 23:59 on the date of last study visit

Table 4: Analysis Period Definitions (Extension Phase)

Phase	Period	Interval	
		From	To
eFollow-up 2		One minute after Follow-up 2 phase ends	One minute prior to signing the informed consent form
eScreening		Date and time of signing the informed consent form	One minute prior to start of post dose 1 period
eRegimen	ePost-dose 1	Date and time of first vaccination	Minimum of: e) 23:59 on the date of last contact (for early discontinuation) f) 23:59 of 28 days after the first vaccination (23:59 of day of vaccination + 28 days) g) One minute prior to ePost-dose 2 period
eFollow-up 1		One minute after ePost-dose 1 period ends	Minimum of: d) 23:59 on the date of last contact (for early discontinuation) e) One minute prior to ePost-dose 2 period
eRegimen	ePost-dose 2	Date and time of second vaccination	Minimum of: d) 23:59 on the date of last contact (for early discontinuation) e) 23:59 of 28 days after the second vaccination (23:59 of day of vaccination + 28 days)
eFollow-up 2		One minute after ePost-dose 2 period ends up to 28 days after last post-dose.	Minimum of: d) 23:59 on the date of last contact (for early discontinuation) e) 23:59 on the date of last study visit

2.2. Pooling Algorithm for Analysis Centers

There are two sites in this study and the data from the two sites involved will be pooled for analysis.

2.3. Analysis Sets

Vaccination assignment will follow the "as treated" principle. That is, participants will be analyzed according to the actual intervention received.

2.3.1. Full Analysis Set (FAS)

The full analysis set will include all participants with at least one study intervention administration documented.

2.3.2. Per Protocol Immunogenicity Population (PPI)

The per-protocol immunogenicity population will include all randomized and vaccinated participants for whom immunogenicity data are available excluding participants with major protocol deviations expecting to impact the immunogenicity outcomes (eg, missed Dose 2 vaccination, natural infections, etc.). In addition, the following will be considered for the immunogenicity analysis:

- Immunogenicity samples of participants obtained after missed doses (or out-of-window Dose 2 vaccinations), samples obtained after natural infection (if applicable) or samples obtained outside the protocol-defined window will be excluded in graphs and tables

showing descriptive statistics. These measurements will however be shown in listings, together with the indication that they are not used in the analysis.

- The immunogenicity analysis will be repeated on the full analysis set to evaluate the robustness of the analysis results, if more than 10% of participants from the full analysis set are excluded from the per protocol immunogenicity population.

2.4. Definition of Subgroups

There are 2 age groups (ie, ≥4 to ≤8 months, and >8 to <12 months of age) in this study and the study data (participant information, safety and immunogenicity) will be presented by these age groups. The study data will also be presented pooled over these 2 age groups.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

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

For the main study, an independent data monitoring committee (IDMC) will be instituted prior to the start of the study. The IDMC will periodically review safety data to ensure progressive safety of the participants. Enrollment of participants will start with vaccination of a sentinel cohort of 16 infants before exposing the remainder of the infants to the study intervention. The IDMC will review data of the sentinel cohort. Progression to the enrolment of the remainder of the participants will be based on the favorable IDMC review of the safety data of the sentinel cohort of 16 infants. Ad-hoc IDMC meetings may also be requested via the sponsor for any single event or combination of multiple events which are considered to jeopardize the safety of the participants. See the IDMC charter[2] and the associated SAP[3] for further details.

For all cases, the data package and analysis results that contained any piece of unblinding information will be kept in a strictly confidential place, with access for IDMC and the independent statistical support group members only until unblinding of the study by the sponsor.

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

4. SUBJECT INFORMATION

Participant information will be shown for the full analysis set. In general, the data will be presented by age group (in months) and intervention arm. This information will be shown for the main study, as well as for the extension phase. The extension phase consists of all participants in the control arm giving consent to continue in this extension phase. That means the population in the extension phase is a subpopulation of the control arm of the main study.

4.1. Demographics and Baseline Characteristics

For both main study and extension phase, demographic and screening/baseline characteristics will be tabulated and summarized with descriptive statistics per vaccine intervention arm and over all participants. The following demographic and baseline characteristics will be summarized.

- Sex (Female/Male)
- Age (months)
- Race
- Ethnicity
- Height (Body length in cm)
- Weight (kg)
- Baseline EBOV-GP binding antibody response (EU/mL) status.
- Weight-for-age percentile at baseline, using WHO Child Growth Standards (birth to 24 months)[4].

To obtain the weight-for-age percentile for the participants, the z-score (z) will first be determined as:

$$z = \frac{\left(\left(\frac{weight}{M}\right)^{L} - 1\right)}{(S \times L)}.$$

Where L, M and S denote the power in the Box-Cox transformation, median and generalized coefficient of variation, respectively. The L, M and S are the values from the appropriate WHO table[4] corresponding to the age in months of the child. The percentile corresponding to the calculated z-score will then be obtained based on the Standard Normal distribution.

For example, to obtain the weight-for-age z-score of a 4-month-old male who weighs 7.5 kg, the L, M and S values from the appropriate (Weight-for-age tables: WHO Child Growth Standards Data File[4]) table are L= 0.1553, M=7.0023, and S=0.11316. Using the above formula, the calculated z-score for this child is 0.4173029. This z-score corresponds to the 66th percentile.

4.2. Disposition Information

For both main study and extension phase, the number and percentage of participants screened, participants in the full analysis set, participants vaccinated but not randomized, participants randomized but not vaccinated, participants who received MenACWY as third vaccination, participants who completed (study completion and vaccination completion) and discontinued participants (study discontinuation and vaccination discontinuation) with the reason of discontinuation will be tabulated per intervention arm and overall. Also, the number of participants and percentage in each analysis period will be tabulated.

4.3. Treatment Compliance

For both main study and extension phase, the number and percentage of participants receiving the second vaccination within the protocol defined windows will be summarized.

4.4. Protocol Deviations

For both main study and extension phase, major protocol deviations will be summarized by deviation category. A listing of the major protocol deviations will also be generated. The deviations that have the potential to influence immune response will be flagged in the listing.

4.5. Concomitant Medications

The analysis of concomitant therapies will be done using the World Health Organization (WHO) drug coding terms. If the coded term for a concomitant medication is missing, then the reported term will be used and flagged in the table. For both main study and extension phase, the concomitant therapies will be tabulated per analysis period. Additionally, a listing of all pre-study and concomitant therapies will be provided. There will be special attention to analgesics/antipyretics (such as acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDs] and aspirin) administered during the first 8 days (including the day of the vaccination) following each vaccination.

Based on their start and stop date, concomitant therapies will be reported in each applicable analysis period. If a concomitant therapy record misses components of its start and/or stop dates (day and/or month and/or year), then they will be assigned as follows:

- In case of partial start or stop dates, the concomitant therapy records will be allocated to periods using the available partial information, without imputations. If, for example, only month and year are available, these will be compared to the month and the year of the periods, and the concomitant therapy record will be allocated to the period(s) where these date parts match. This rule may lead to assignment to multiple periods.
- In case of a completely missing start date, the concomitant therapy will be considered as having started before the trial.
- In case of a completely missing end date, the concomitant therapy will be considered as ongoing at the end of the trial.

Remark: In addition to the date information, time information is considered to allocate concomitant therapies to analysis periods, if available.

5. SAFETY

Safety analyses will be performed on the full analysis set. Continuous variables will be summarized using the following statistics, as appropriate: number of observations, arithmetic mean (mean), 95% CI for the mean, standard deviation (SD), standard error (SE), median, quartiles (Q1 and Q3), minimum and maximum. Frequencies and percentages (one decimal place) will be generated for categorical variables. No formal comparisons between groups will be provided.

The safety data will be presented by vaccine regimens (ie, intervention arms) as described in the study protocol. The data will be presented by analysis period (post-dose 1 and post-dose 2) as well as over the entire regimen period (ie, combined post-dose 1 and post-dose 2 periods). Denominator for the percentages will be the number of participants in the considered population and period/phase for a certain regimen (eg, incidence per 100 participants/period).

5.1. Adverse Events (AE)

5.1.1. Definitions

Solicited AEs shown in the tables will be extracted from the investigator assessment pages of the eCRF. For unsolicited AEs, only the AEs within the 28-day period following each vaccination will be presented in the safety tables except for SAE, which will be captured and tabulated in the outputs covering the entire study duration. A listing will also be generated for all collected unsolicited adverse events.

Solicited local AEs will be considered (by definition) as related to the study vaccine. The severity of the AEs will be classified as Grade 1 to 4. In case no grades are available, the grading of the solicited events will occur according to the grading list in Attachment 1.

The main study outputs will present AEs for both the Ebola vaccination regimen as the control arm. At the end of the extension phase, AEs are presented for the participants of the control arm receiving the Ebola vaccination regimen. Listings will show all AEs of both parts of the study, adding a column showing main study/extension phase. Tabulations will be done for each phase separately.

5.1.2. Analysis of Adverse Events

Number and percentage of participants with at least one particular AE (unsolicited/solicited) will be tabulated. Unsolicited AEs will be summarized by System Organ Class and Preferred Term. Solicited AEs will be summarized by class (local, systemic) and preferred term.

The following tables will be generated for solicited AEs: summary, by worst severity grade, at least Grade 3, related (systemic only), time to onset (in days) and duration (in days) for most frequent events and body temperature. Note that duration is defined as number of days from the start of the event until resolution of the event. The time to first onset is defined as (date of first onset – reference date + 1). The reference date is the start date of the vaccination period.

For unsolicited AEs, the following tables will be generated: summary table (including SAE, AE with fatal outcome, AEs leading to study discontinuation, and AEs leading to discontinuation of study vaccination), all events, most frequent, grade 3, permanent stop of vaccination, related and SAE.

Listings and/or participant narratives will be provided as appropriate, for those participants who die, discontinue study vaccinations due to an AE, or experience a severe or serious AE.

5.1.3. Phase allocation of Adverse Events

Solicited events are always allocated to the respective Post Dose period. Adverse events in the SDTM database are allocated to periods based on their start date/time. If the start date/time of an event falls between (or on) the start and stop date/time of a period, the AE is attributed to that period (treatment-emergent principle). A stepwise approach to allocate adverse events to the analysis periods/phases based on their start date/time is given in Attachment 2.

5.1.4. Missing Data

Missing data will not be imputed. Participants who do not report an event will be considered as participants without an event. An AE with a missing severity or relationship will be considered as an AE reported, but will be considered as not reported for the severity or relationship. For example, an AE with missing severity will be considered as an AE reported for the analysis of any grade, but will be considered as not reported for the analysis of grade 3.

5.2. Laboratory, Vital Signs and Physical Examinations

Laboratory abnormalities will be determined according to the toxicity grading tables (see Attachment 1), and in accordance with the normal ranges of the clinical laboratory. Laboratory and vital signs abnormalities/toxicities will not be summarized since assessments are only done at screening and pre-dose 2. Clinically significant abnormal laboratory data reported in the CRF will be presented in the data listings.

A full physical examination is only conducted at screening. At other visits, only abbreviated, symptom-directed examinations are performed per the investigator's discretion and the clinically significant abnormal findings are recorded as AEs. Therefore, separate analysis of physical examination findings will not be performed.

6. IMMUNOGENICITY ANALYSIS

6.1. Parameters

Humoral immune responses as measured by the following assays will be analyzed:

- Binding antibody responses using Filovirus Animal Nonclinical Group (FANG) ELISA: Quantification of antibodies binding to EBOV GP using the EU/mL readout.
- Neutralizing antibody response against the adenovirus backbone (Ad26 VNA)

6.2. Handling of Missing and/or Unquantifiable Immune Response Data

For both ELISA binding antibody responses (EU/mL) and Ad26 VNA (IC_{90} Titer), values below the respective lower limit of quantification (LLOQ) will be imputed with half of the corresponding LLOQ (ie, LLOQ/2) and values above the upper limit of quantification (ULOQ) will be imputed with the ULOQ. For the calculation of fold changes (if applicable), the values below LLOQ will be imputed with the corresponding LLOQ and values above the ULOQ will be imputed with the ULOQ.

6.3. Immune Response Analysis

No formal hypothesis on immunogenicity will be tested.

6.3.1. Immunogenicity Against the Insert:

6.3.1.1. Humoral Assays

The following will be defined for binding antibody responses as measured by EBOV GP Filovirus Animal Nonclinical Group (FANG) ELISA (EU/mL):

- **Sample interpretation:** A sample will be considered positive, if the value is above the LLOQ.
- **Responder:**
  - If sample interpretation is negative at baseline but positive post-baseline and the post-baseline value is greater than 2.5×LLOQ; OR
  - If sample interpretation is positive at both baseline and post-baseline and there is a greater than 2.5-fold increase from baseline (2.5-fold increase on the original scale).

The analysis of binding antibody responses (EU/mL) will be presented by age category per intervention arm. The following outputs will be generated:

- Table of summary statistics (ie, geometric means and corresponding 95% CIs, geometric mean fold increase [from Pre-dose 1] with corresponding 95% CI), responder rates and positive sample interpretation (ie, showing number, percentage and the exact 95% Clopper-Pearson CI).
- Table of summary statistics (ie, geometric means and corresponding 95% CIs, geometric mean fold increase [from Pre-dose 1] with corresponding 95% CI), responder rates and positive sample interpretation (ie, showing number, percentage and the exact 95% Clopper-Pearson CI) by pre-existing antibody response against Ad26 vector (ie, pre-existing Ad26 versus no pre-existing Ad26).
- Graphic (on a $\log_{10}$-scale) of regimen profiles of the geometric mean concentrations with 95% CIs.
- Graphic (on a $\log_{10}$-scale) of regimen profiles of the geometric mean concentrations with 95% CIs by pre-existing antibody response against Ad26 vector (ie, pre-existing Ad26 versus no pre-existing Ad26).
- Dot plots (on a $\log_{10}$-scale) with distinction between positive and negative sample interpretations.
- Data listing.

6.3.2. Immunogenicity Against the Vector

For the analysis of the immunogenicity against Ad26 vector (backbone), a sample value will be considered positive if it is above the assay LLOQ. The data will be presented as follows:

- Table of summary statistics (geometric means and its corresponding 95% CIs) and positive sample interpretation (ie, showing number, percentage and the exact 95% Clopper-Pearson CI).
- Dot plots (on a $\log_{10}$-scale) with distinction between positive and negative sample interpretations
- Scatter plot (on a $\log_{10}$-scale) with Spearman's correlation coefficient of 21 days post-dose 2 binding antibody responses (EU/mL) against baseline Ad26 vector neutralization antibodies.
- A data listing

REFERENCES

1. VAC52150EBL2005 Protocol Amendment 3: A Phase 2 Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of a Heterologous 2-dose Vaccination Regimen Using Ad26.ZEBOV and MVA-BN®-Filo in Infants Aged 4-11 Months in Guinea and Sierra Leone. London School of Hygiene and Tropical Medicine, Institut National de la Santé et de la Recherche Médicale, University of Antwerp, College of Medicine and Allied Health Sciences, and Janssen Vaccines & Prevention B.V. (1 October 2019).
2. VAC52150EBL2005 Independent Data Monitoring Committee Charter. Janssen Vaccines & Prevention B.V. (July 2019)
3. VAC52150EBL2005 Independent Data Monitoring Committee Statistical Analysis Plan. Janssen Vaccines & Prevention B.V. (July 2019)
4. WHO Child Growth Standards (birth to 24 months). Available at: https://www.who.int/childgrowth/standards/weight_for_age/en/. Accessed April 2019.
5. VAC52150EBL2005 Protocol Amendment 3: A Phase 2 Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of a Heterologous 2-dose Vaccination Regimen Using Ad26.ZEBOV and MVA-BN®-Filo in Infants Aged 4-11 Months in Guinea and Sierra Leone. London School of Hygiene and Tropical Medicine, Institut National de la Santé et de la Recherche Médicale, University of Antwerp, College of Medicine and Allied Health Sciences, and Janssen Vaccines & Prevention B.V. (28 September 2021).

ATTACHMENTS

1. TOXICITY GRADING SCALE FOR HEALTHY PEDIATRIC PARTICIPANTS UP TO 3 YEARS OF AGE ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS

Adapted from: Division of Microbiology and Infectious Diseases (DMID Pediatric Toxicity Tables (November 2007, draft). For adverse events not included in the tables below, refer to the severity criteria guidelines in Section 12.1.3 of the CTP. Local lab references take preference over the DMD table and the different grades. The abbreviations used in the following tables are: LLN: lower limit of normal; IV: intravenous; ULN: upper limit of normal.

LOCAL REACTIONS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Tenderness	Mild discomfort to touch; minimal to no limitation of use of limb	Notable discomfort to touch; Greater than minimal limitation of use of limb	Significant discomfort at rest; Severe limitation of use of limb	Hospitalization or ER visit for treatment
Erythema	<10 mm	10-25 mm	26-50 mm	>50 mm or any grade 3 with hospitalization or ER visit for treatment
Swelling	<10 mm	10-25 mm	26-50 mm	>50mm or any grade 3 with hospitalization or ER visit for treatment
HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin for children greater than 3 months and less than 2 years of age	9.0-9.9 gm/dL	7.0-8.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to Anemia
Hemoglobin for children greater than 2 years of age	10.0-10.9 gm/dL	7.0-9.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to Anemia
Absolute Neutrophil Count	750-1200/mm^3	400-749/mm^3	250-399/mm^3	<250/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	25,000-49,999/mm^3	<25,000/mm^3
Prothrombin Time (PT)	1.1-1.2 x ULN	1.3-1.5 x ULN	1.6-3.0 x ULN	>3.0 x ULN
Partial Thromboplastin Time (PTT)	1.1-1.6 x ULN	1.7-2.3 x ULN	2.4-3.0 x ULN	>3.0 x ULN
GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bilirubin (Fractionated bilirubin test must be performed when total bilirubin is elevated)				
Bilirubin for children greater than 3 months of age (when accompanied by any increase in other liver function test)	1.1- <1.25 x ULN	1.25- <1.5 x ULN	1.5-1.75 x ULN	>1.75 x ULN
Bilirubin for children greater than 3 months of age (when	1.1- <1.5 x ULN	1.5- <2.0 x ULN	2.0-3.0 x ULN	>3.0 x ULN

other liver functions are in the normal range)				
AST (SGOT)	1.1- <2.0 x ULN	2.0- <3.0 x ULN	3.0-8.0 x ULN	>8.0 x ULN
ALT (SGPT)	1.1- <2.0 x ULN	2.0- <3.0 x ULN	3.0-8.0 x ULN	>8.0 x ULN
GGT	1.1- <2.0 x ULN	2.0- <3.0 x ULN	3.0-8.0 x ULN	>8.0 x ULN
Pancreatic Amylase	1.1- 1.4 x ULN	1.5- 1.9 x ULN	2.0-3.0 x ULN	>3.0 x ULN
Uric Acid	7.5-9.9 mg/dL	10.0-12.4 mg/dL	12.5-15.0 mg/dL	>15.0 mg/dL
Loss of Appetite	Feeding minimally reduced	Feeding reduced by more than 50% of normal for the child	Refusing all feeds	No solid or liquid taken orally for in the last 24 hours; requires intravenous fluids
Diarrhea	Change in consistency of stools OR increase of 1-3 stools over baseline per 24-hour period	liquid/watery stools OR increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥7 stools over baseline per 24-hour period	Requires IV fluid resuscitation and electrolytes repletion OR hypotensive shock
Constipation	Slight change in consistency and/or frequency of stools	Hard, dry stools with a change in frequency	Intestinal obstruction accompanied with abdominal pain	Hospitalization; Severe abdominal distention and vomiting accompanied with severe abdominal pain
Vomiting	1 episode/ day (24h)	2-3 episodes per day (24h)	4-6 episodes per day (24h)	Greater than 6 episodes per day (24h) OR intractable vomiting
ELECTROLYTES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine				
3 Months – 2 Years of age	0.6-0.8 x ULN	0.9-1.1 x ULN	1.2-1.5 x ULN	> 1.5 x ULN
2 Years – 3 Years of age	0.7-1.0 x ULN	1.1-1.6 x ULN	1.7-2.0 x ULN	>2.0 x ULN
Hypernatremia	----	145-149 mEq/L	150-155 mEq/L	>155 mEq/L or abnormal sodium AND mental status changes
Hyponatremia	----	130-135 mEq/L	129-124 mEq/L	<124 mEq/L or abnormal sodium AND mental status changes
Hyperkalemia	5.0-5.9 mEq/L	6.0-6.4 mEq/L	6.5-7.0 mEq/L	>7.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypokalemia	3.0-3.5 mEq/L	2.5-2.9 mEq/L	2.0-2.4 mEq/L	<2.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypercalcemia	10.5-11.2 mg/dL	11.3-11.9 mg/dL	12.0-12.9 mg/dL	>13.0 mg/dL
Hypocalcemia	7.8-8.4 mg/dL	7.0-7.7 mg/dL	6.0-6.9 mg/dL	>6.0 mg/dL
Hypomagnesemia	1.2-1.4 mEq/L	0.9-1.1 mEq/L	0.6-0.8 mEq/L	<0.6 mEq/L or abnormal magnesium AND cardiac arrhythmia

hypoglycemia	55-65 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or adnormal glucose AND mental status changes
Hyperglycemia	116-159 mg/dL	160-249 mg/dL	250-400 mg/dL	>400 mg/dL or ketoacidosis
Proteinuria	Tr-1+ or <150 mg/day	2+ or 150-499 mg/day	3+ or 500-1000 mg/day	4+ or Nephrotic syndrome >1000 mg/day
Hematuria	Microscopic <25 cells/hpf	Microscopic >25 cells/hpf	Gross hematuria	Hospitalization; Life-threatening consequences
Neurologic				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Irritability	Easily consolable; minimal or no interference with activity. Episodes of continuous crying <60 min.	Difficult to console. Episodes of continuous crying >60 min <120 min	Inconsolable, prevents daily activity. Episodes of continuous crying >120 min	Hospitalization or ER visit for treatment
Decreased Activity	Minimal decrease in alertness, minimal or no interference with activity	Some interference with activity, slightly subdued	unable to achieve normal level of alertness, lethargic	ER visit or hospitalization for treatment or life-threatening consequences
Neuropathy/ Lower Motor Neuropathy	----	Mild transient Paresthesia only	Persistent or progressive paresthesia, burning sensation in feet, or mild dysesthesia; no weakness; mild to moderate deep tendon reflex changes; no sensory loss	Onset of significant weakness, decrease or loss of DTRs, sensory loss in "stocking glove" distribution, radicular sensory loss, multiple cranial nerve involvement; bladder or bowel dysfunction, fasciculations, respiratory embarrassment from chest wall weakness.
Myopathy or Neuromuscular Junction Impairment	Normal or mild (<2 x ULN) CPK elevation	Mild proximal weakness and/or atrophy not affecting gross motor function. Mild myalgias, +/- mild CPK elevation (<2 x ULN)	Proximal muscle weakness and/or atrophy affecting motor function +/- CPK elevation; or severe myalgias with CPK >2 x ULN;	Onset of myasthenia-like symptoms (fatigable weakness with external, variable ophthalmoplegia and/or ptosis), or neuromuscular junction blockade (acute paralysis) symptoms
OTHER				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Fever/pyrexia	38.0 - 38.4 °C or 100.4 - 101.1 °F	38.5 - 38.9 °C or 101.2 - 102.0 °F	39.0 - 40.0 °C or 102.1 - 104.0 °F	Greater than 40 °C or 104.0 °F

Acute allergic reaction	Pruritus without Rash	Pruritic Rash	Mild Urticaria	Severe Urticaria Anaphylaxis, Angioedema
Stomatitis	Mild discomfort	Painful, difficulty swallowing, but able to eat and drink	Painful: unable to swallow solids	Painful: unable to swallow liquids; requires IV fluids
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Hospitalization

2. PERIOD/PHASE ALLOCATION OF ADVERSE EVENTS

Solicited events are always allocated to the respective Post Dose period. Adverse events will be allocated to analysis periods/phases by following the following steps:

Step 1: Allocation of events to the periods:

Adverse events in the SDTM database are allocated to periods/phases based on their start date/time. If the start date/time of an event falls between (or on) the start and stop date/time of a period, the AE is attributed to that period (treatment-emergent principle).

– In case of partial start or stop dates (i.e. time and/or day and/or month and/or year missing), the events are allocated to the periods using the available partial information on start and end date; no imputation will be done. If, for instance, the AE start date only month and year are available, these data are compared to the month and year information of the periods. This rule may lead to multiplication of the event as a consequence of its assignment to multiple periods.

– In case of a completely missing end date, the date is imputed by the cut-off date of the analysis for participants still ongoing in the study, and by the end date of the last period for participants who discontinued or completed the trial. In case of a completely missing start date, the event is allocated to the first active treatment phase (post dose 1 period), except if the end date of the AE falls before the start of the first active treatment phase (post dose 1 period).

Step 2: Combination of events:

Overlapping/consecutive events are defined as events of the same subject with the same preferred term which have at least 1 day overlap or for which the start date of an event is 1 day after the end date of the preceding event. Overlapping/consecutive events may be combined into one AE or not, according to the following rules:

1) If overlapping/consecutive events start in one of the following periods - Screening or post dose extension (i.e. non-active periods) - followed by an AE in - post-dose period (active period) - they are allocated to their respective periods and are considered as separate events.

2) In case overlapping/consecutive events start within a single period, they are considered as one and the same AE. The individual events which contribute to this AE are retained as individual

records in the ADaM database but are assigned the same onset, period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.

3) In case overlapping/consecutive events start in both an active period followed by a non active period, they are allocated to the active period only and are considered as one and the same AE. The individual events which contribute to this AE are retained as individual records in the ADaM database but are assigned the same onset, treatment period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.

4) In case an active period is followed by another active period, and the overlapping/consecutive events start in both periods, they are allocated to their respective period and are considered as separate AEs. The same rule applies for 2 non-active periods.

Remarks:

1. Events can only be combined into one and the same AE if their start and stop dates are known.

2. In case the completely missing end date is imputed (for period allocation), this date is also considered as a complete date.

3. Time is not considered when determining overlap of events.