Janssen Vaccines & Prevention

Statistical Analysis Plan
(Primary, Interim and Final Analyses)

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

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

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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

Version	Date	Description
1.0	20 April 2020	Initial version
2.0	17 June 2020	Amendment 1 (this document)

The overall rationale for Amendment 1: The purpose for this amendment is to align with protocol Amendment 3 and to incorporate the COVID-19 related information into the specific analyses following the FDA[2] and EMA[3] guidance on the conduct of clinical trials during the COVID-19 pandemic. Also, clarification is given on the inclusion of participants in the immunogenicity subset due to protracted contract negotiations for 1 site resulting in the inability of the site to participate in the study. The changes made together with the rationales are as follows:

Rationale: Because of the recent (on 11 March 2020) WHO-declared COVID-19 pandemic, some study participants are affected in one way or the other (eg, missed Dose 2 vaccination, out-of-window visits, etc.). The study protocol has been amended to address the impact on the ability of participants to return within window (±3 days) for Dose 2 in this lot-to-lot consistency study and proposed to widen the window to -3/+28 days, while maintaining the ability to achieve the primary and secondary objectives of the study. The change (ie, from ±3 days to -3/+28 days) in the window around the Dose 2 vaccination visit is clarified. Also, additional analyses will be needed to incorporate the COVID-19 related information in the clinical study report. Information is therefore included for potential COVID-19 related analyses.

1.2 Trial Design
4.3 Vaccination Compliance
4.4 Protocol Deviations
4.5 Concomitant Medications
5.1 Adverse Events

Rationale: The first 456 participants (144 in each of Groups 1 to 3 and 24 in Group 4) in the main study were to be assessed for immunogenicity (immunogenicity subset). For operational feasibility, the first 57 from each of 8 study sites (ie, 57 out of a total of 93 participants per site) were to be included in the immunogenicity subset. However, protracted contract negotiations for 1 site resulted in the inability of the site to participate in the study. Therefore, it was decided to redistribute the allotment of 93 participants to the sites that nearly completed enrollment for their original allotment including the remaining 57 participants to be included in the immunogenicity subset. Due to an oversight, the immunogenicity subset slots were not opened in IWRS resulting in all remaining 93 participants being randomized in the safety only cohort. Therefore, there was no baseline immunogenicity sample obtained for any of these participants. It is clarified that the last 57 participants in the main study who were initially for safety only will be included in the immunogenicity subset to ensure that at least 456 participants are part of the immunogenicity subset and to limit the potential imbalance in the number of participants in each group for the primary and secondary hypothesis testing.

1.6. Changes to Planned Analyses

Rationale: A full physical examination is only conducted at screening and any abnormality is recorded on the medical history form. At other visits, only abbreviated, symptom-directed examinations are performed and the clinically significant abnormal findings are recorded as AEs. Information is added to clarify that these records captured as medical history will only be included in the medical history analysis and those captured as AEs will be analyzed as AEs.

1.6 Changes to Planned Analyses

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

ABBREVIATIONS

Ad26	adenovirus serotype 26
AE	adverse event
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
CTP	clinical trial protocol
EBOV	Ebola virus
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EU	ELISA units
GMC	geometric mean antibody concentration
FDA	Food and Drug Administration
GP	glycoprotein
IWRS	interactive web response system
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the analyses that are planned for the study VAC52150EBL3004. These analyses will be performed for the respective database locks when:

- All participants in Groups 1-4 have completed the 28-day post Dose 2 time point visit or discontinued earlier (primary analysis).
- All participants in Groups 1-4 have completed the 6-month post Dose 2 visit (ie, the last study-related visit) or discontinue earlier (interim analysis)
- All participants in Groups 5-6 have completed the 28-day post booster dose time point visit or discontinued earlier (interim analysis).
- All participants in the study have completed the last study-related visit or have discontinued earlier (final analysis).

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).

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 Amendment 3 (CTP)[1].

Table 1: Study 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 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)

• 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.

1.2. Trial Design

Study VAC52150EBL3004 is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase 3 study with the primary objective 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 (ie, Lots A, B and C) at a nominal dose of $5x10^{10}$ viral particles (vp) as Dose 1 and 3 consecutively manufactured lots of MVA-BN-Filo (ie, Lots 1, 2 and 3) at a nominal dose of $1x10^{8}$ infectious units (Inf U) as Dose 2 at a 56-day interval in adult (18-50 years) participants. 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 is to receive 2 placebo vaccinations administered at a 56-day interval. Once randomization to Groups 1-4 is completed, an additional Booster Cohort of approximately 60 participants will be enrolled. 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). A schematic overview of the study design and groups is provided in Table 2.

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 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%) is expected to 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.

Depending on the extent of the COVID-19 impact on the study, additional participants will be recruited in the immunogenicity subset. For instance, 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 original protocol-defined windows (±3 days) for Dose 2 administration. Investigators were then 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 some

participants are returning to the sites for follow-up. In order to reduce the number of additional participants needed for the primary and secondary immunogenicity analyses without jeopardizing the evaluation of the primary and secondary objectives of the study, the window around Dose 2 administration for the main part of the study (Groups 1-4) was widened in CTP Amendment 3[1]. In particular, the upper limit of the window around Day 57 (Dose 2) was extended to Day 85 (ie, Day 57+28 days). The widening of window was deemed acceptable after examination of the immunogenicity data from previous studies (ie, VAC52150EBL2001 and VAC52150EBL2002) in which Dose 2 was administered at intervals ≥56 days. Although there appears to be a trend of increasing GMCs with increasing intervals between Dose 1 and Dose 2 from those studies, 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 log10-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. See CTP Amendment 3[1] for further details. Unless otherwise mentioned in this document, the "protocol-defined window" refers to the visit windows as defined in CTP Amendment 3[1].

For the Booster Cohort (Groups 5-6), a planned total of 60 participants will be enrolled. All participants in the booster 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). For further details, see Sections 3 and 6 of the CTP Amendment 3[1].

Table 2: Schematic Overview of Study Design and Groups

Groups	N	Dose 1	Dose 2	Booster
		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

1.3. Statistical Hypotheses for Trial Objectives

1.3.1. Primary Hypothesis

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 concentrations 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 concentrations 21 days post Dose 2, for all 3 pairwise comparisons (ie, Groups 1 versus [vs] 2, 1 vs 3, and 2 vs 3 [see overview of the groups in Table 2]).

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 and are expected to be adequate to detect potential clinically meaningful differences in GMCs. 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) will be established if equivalence is shown for all 3 pairwise comparisons.

1.3.2. Secondary Hypothesis

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

1.4. Sample Size Justification

The following assumptions were 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 was 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 were 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 GMCs. This relative difference is based on both the process variability in vp content of the Ad26.ZEBOV lots and Inf U content of the 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 was used for the sample size calculation. 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). In addition, approximately 60 participants will be randomized in a 5:1 active:placebo ratio (Group 5:Group 6), to provide a reasonable estimation of the humoral immune response to a booster dose.

1.5. Randomization and Blinding

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of the 6 vaccination groups 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. The IWRS will assign a unique code, which will dictate the study vaccine assignment and matching study vaccine kit for the 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 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 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. 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

- In the main part of the study (Groups 1-4), a planned total number of at least 741 participants were to be enrolled with the first 456 participants (144 in each of Groups 1 to 3 and 24 in Group 4) to be included in the immunogenicity subset and the remaining 285 for safety only (see CTP Sections 3.1 and 11.2 for details). Due to operational feasibility, the first 57 out 93 participants from each of 8 study sites were to be included in the immunogenicity subset. Protracted contract negotiations for 1 site resulted in the inability of the site to participate in the study. Therefore, it was decided to redistribute the allotment of the 93 participants to the sites that nearly completed enrollment for their original allotment and 57 of these were to be included in the immunogenicity subset. However, there was an oversight and immunogenicity subset slots were not opened in IWRS resulting in all remaining 93 participants being randomized in the safety only cohort. Therefore, there was no baseline immunogenicity sample obtained for any of these participants. In order to ensure that 456 participants are part of the immunogenicity subset and to limit the potential imbalance in the number of participants in each group for the primary and secondary hypothesis testing, the last 57 participants in the main study who were initially for safety only will be included in the immunogenicity subset.

- A full physical examination is only conducted at screening and any abnormality is recorded on the medical history form of the eCRF. 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. Accordingly, physical examination findings will only be included in the analysis of medical history and AEs.

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, Groups 1, 2, 3, 4, 5 and 6). Also, participants who receive only the first

vaccination (Ad26.ZEBOV or placebo) will be included in accordance with the randomization group 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, 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 to 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 value*.

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 analysis that will be presented by time point (eg, 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

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 primary (or interim) analysis 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

Phase	Period	Interval	
		From	To
Post-dose 1 FU		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 primary (or interim) analysis 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 primary (or interim) analysis c) 23:59 of 28 days after the second vaccination (23:59 of day of vaccination + 28 days)
Post-dose 2 FU		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 primary (or interim) analysis c) 23:59 on the date of last study visit d) One minute prior to post-dose 3 period
Regimen	Post-dose 3	Date and time of third 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 third vaccination (23:59 of day of vaccination + 28 days)
Post-dose 3 FU		One minute after post-dose 3 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 primary (or interim) analysis c) 23:59 on the date of last study visit

FU: Follow-up
Note: Dose 3 corresponds to booster vaccination.

2.2. Pooling Algorithm for Analysis Centers

There is more than 1 site in this study and data from the different sites 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 vaccine received.

2.3.1. Full Analysis Set

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

2.3.2. Per Protocol Analysis Set

The per protocol analysis set for the main part of the study (Groups 1-4) 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. 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 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.

Note that the per protocol analysis set will only be defined for participants included in the immunogenicity subset and the booster cohort. The following will be considered for the immunogenicity analysis based on the per protocol analysis set:

- The primary and secondary hypotheses will be based on those in the set with data at 21 days post Dose 2 and 56 days post Dose 1, respectively. Participants who will receive incorrect batch (other than the one randomized to) of vaccination will only be excluded from these hypothesis tests.
- Immunogenicity samples obtained after missed doses (or out-of-window Dose 2 or Dose 3 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.
- If more than 10% of participants from the full analysis set are excluded from the per protocol analysis set, then the immunogenicity analysis (including both primary and secondary hypothesis testing) will be repeated on the full analysis set to evaluate the robustness of the analysis results.
- The upper limit of the window around Day 57 (Dose 2) was extended to Day 85 (ie, Day 57+28 days) in the main part of the study (Groups 1-4) in order to reduce the number of additional participants needed for the primary and secondary immunogenicity analyses. Therefore, both the primary and secondary objectives (based on data of only participants in the per protocol analysis set who received the second vaccination within the original window [±3 days] around the Day 57 visit) will be assessed as sensitivity analyses (albeit with reduced power for testing the hypotheses).

2.4. Definition of Subgroups

Subgroup analyses will be performed for participants who will receive delayed (due to COVID-19 pandemic) Dose 2 vaccination:

- If more than 10% of participants in the immunogenicity subset receive their second vaccination outside the widened (ie, -3/+28 days) window (as defined in CTP Amendment 3[1]) of Day 57, then the immunogenicity analysis will be performed to evaluate the potential impact of delayed (ie, outside the widened window) Dose 2 vaccination on the immune response.
- Similarly, if more than 10% of all participants receive their second vaccination outside the widened window (as defined in CTP Amendment 3[1]), then analysis will be performed to evaluate the potential impact of delayed (ie, outside the widened window) Dose 2 vaccination on safety measures.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

The current SAP is applicable to the primary, interim and final analyses:

- The primary safety and immunogenicity analyses will be performed when all participants in Groups 1-4 have completed the 28-day post Dose 2 visit or discontinued earlier, and the database is locked. This analysis will include all available data up to this point. Only sponsor personnel not involved in the review and determination of causality of serious adverse events (SAEs) 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 SAEs 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.

A multidisciplinary Safety Management Team (SMT) is in place for the development of the Ebola vaccine 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 and MVA-BN-Filo. Refer to CTP[1] Section 9.3 for details.

4. SUBJECT INFORMATION

Participant information will be shown for the full analysis set. In general, the data will be presented by vaccination group.

4.1. Demographics and Baseline Characteristics

Demographic and screening/baseline characteristics will be tabulated and summarized with descriptive statistics per vaccination group (as shown in Table 2) and over all participants. The following demographic and baseline characteristics will be summarized:

- Sex (Female/Male)
- Age (years)
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI, kg/m^2), calculated from the recording of baseline height and weight
- Baseline EBOV-GP binding antibody (EU/mL) positivity, only for the immunogenicity subset and the booster cohort
- Positivity of baseline viral neutralizing antibody (VNA) against the Ad26 vector (IC_{90} titers), only for the booster cohort

4.2. Disposition Information

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 completed

(study completion and vaccination completion) and discontinued participants (study discontinuation and vaccination discontinuation) with the reason of discontinuation will be tabulated per vaccination group and overall. Also, the number of participants and percentage in each analysis period will be tabulated.

4.3. Vaccination Compliance

The number and percentage of participants receiving the second vaccination within (and outside) the ±3 days and -3/+28 days windows will be summarized. Also, a summary and/or listing of participants who missed second vaccination or received it outside the protocol-defined window due to the COVID-19 pandemic will be generated.

4.4. Protocol Deviations

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. In addition, all COVID-19 related protocol deviations (ie, both major and minor deviations) will be summarized and/or listed.

4.5. Concomitant Medications

The analysis of concomitant therapies will be done using the World Health Organization (WHO) drug coded terms. If the coded term for a concomitant medication is missing, then the reported term will be used and flagged in the table. 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. Special attention will also be given to all COVID-19 related concomitant therapies, if applicable.

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 will be considered to allocate concomitant therapies to analysis periods, if available.

5. SAFETY

Safety analyses will be performed on the full analysis set. Frequencies and percentages (one decimal place) will be generated for the AEs. No formal comparisons between groups will be provided.

The safety data will be presented by vaccination group (as shown in Table 2). The data will be presented by analysis period (post-dose 1, post-dose 2, and post-booster [only for the booster cohort]) as well as over the entire regimen period (ie, combined post-dose 1 and post-dose 2 periods, and combined post-dose 1, post-dose 2 and post-booster [only for the booster cohort]). Denominator for the percentages will be the

number of participants in the considered analysis set and period/phase for a certain vaccination group (eg, incidence per 100 participants/period).

To evaluate the potential impact of delayed (due to COVID-19 pandemic) Dose 2 vaccination, safety data will also be presented (only if more than 10% of participants receive Dose 2 vaccination outside the widened window) for participants having received Dose 2 vaccination within the widened window (as defined in CTP Amendment 3[1]) versus those having received Dose 2 outside the window.

5.1. Adverse Events

The analysis of AEs will be based on the medical dictionary for regulatory activities (MedDRA) coded terms as will be provided in the clinical database.

5.1.1. Definitions

Solicited AEs shown in the tables will be extracted from the investigator assessment pages of the eCRF. The severity of all AEs will be classified as Grade 1 to 3. For unsolicited AEs, only the AEs within the 28-day period following each vaccination will be presented in the safety tables except for SAEs which will be captured and tabulated covering the entire study duration. A listing will also be generated for all collected unsolicited AEs.

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

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 (ie, any solicited AE, solicited AE with Grade 3 severity, any solicited local AE, solicited local AE with Grade 3 severity, any solicited systemic AE, solicited systemic AE with Grade 3 severity, and solicited systemic AE considered related to vaccine), by worst severity grade, 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 any unsolicited AE, unsolicited AE with severity Grade 1 as worst grade, unsolicited AE with severity Grade 2 as worst grade, unsolicited AE with severity Grade 3 as worst grade, unsolicited AE considered related to vaccine, unsolicited AE leading to permanent stop of study vaccine, SAE, SAE considered related to vaccine, COVID-19 related AE, AEs with fatal outcome), all events, most frequent, Grade 3, AEs leading to permanent stop of vaccination, related and SAE.

Listings and/or participant narratives will be provided as appropriate, for those participants who die, discontinue study vaccination due to an AE, experience a Grade 3 AE considered related to vaccination, experience an SAE, experience a SARS-CoV-2 infection (COVID-19) or vaccine misallocation.

5.1.3. Phase Allocation of Adverse Events

Solicited events are always allocated to the respective post-dose period. The AEs in the standard data tabulation model (SDTM) database will be allocated to periods based on their start date/time. If the start

date/time of an AE 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 AEs 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. Vital Signs and Physical Examinations

Descriptive statistics of vital sign parameters will be summarized at each scheduled time point per vaccination group. 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 and will be analyzed as such. Therefore, no separate analysis of physical examination findings will be performed.

6. IMMUNOGENICITY ANALYSIS

6.1. Parameters

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

- Binding antibody concentrations using Filovirus Animal Nonclinical Group (FANG) ELISA (ie, quantification of antibodies binding to EBOV GP using the EU/mL readout).
- Neutralizing antibodies against the Ad26 vector using an Ad26 VNA readout (IC_{90} titers).

6.2. Handling of Missing and/or Unquantifiable Immunogenicity Data

For the generation of summary statistics, values of the EBOV GP binding antibody concentrations (EU/mL) and Ad26 VNA (IC_{90} titers) that are below the 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 corresponding ULOQ. For the calculation of fold changes, the values below LLOQ will be imputed with the corresponding LLOQ and values above the ULOQ will be imputed with the ULOQ.

6.3. Immunogenicity Data Analysis

6.3.1. Immunogenicity Against the Insert

The following will be defined for binding antibody concentrations as measured by EBOV GP 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).

Primary Analysis

To assess the primary objective, only participants included in the per protocol analysis set will be considered. Estimated differences in the ELISA concentrations (EU/mL) at 21 days post Dose 2 will be

expressed as ratio of GMCs with corresponding 95% CI. This will be determined by comparing log10-transformed binding antibody concentrations (EU/mL) between the groups and back-transformation of the estimated difference and corresponding 95% CI. Equivalence of any 2 groups will be established if the 95% CI of the estimated GMC ratio lies entirely within the range of 0.5 to 2.0. 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) will be established if equivalence is shown for all 3 pairwise comparisons. An analysis of variance model will be used to estimate the GMCs (with the observed binding antibody concentrations [EU/mL] at 21 days post dose 2 as response and group [lot] as the independent variable).

Other Analysis

The secondary objective will be assessed similar to the primary objective, but at 56 days post Dose 1. Equivalence of the 3 different lots of Ad26.ZEBOV (Lots A, B, and C) will be established if equivalence is shown for all 3 pairwise comparisons (Lots A vs B, A vs C and B vs C) at 56 days post Dose 1.

As sensitivity analyses to the widened window around Dose 2 administration for the main part of the study (Groups 1-4) under CTP Amendment 3[1], both the primary and secondary hypotheses will also be tested as sensitivity analysis based only on data of participants who received the second vaccination within the original (ie, ±3 days) window around the Day 57 visit.

The following outputs will also be generated and presented by vaccination groups:

- Table of summary statistics (including geometric means and corresponding 95% CIs, geometric mean fold increase [from Pre-dose 1, Pre-dose 2 and Pre-booster] with corresponding 95% CI), responder rates and positive sample interpretation (ie, showing number, percentage and the exact 95% Clopper-Pearson CI) at all available time points.
- Dot plots (on a $\log_{10}$-scale) with distinction between positive and negative sample interpretations at all available time points.
- Graphic (on a $\log_{10}$-scale) of regimen profiles (ie, geometric mean concentrations with 95% CIs over time).
- Reverse cumulative distribution curve using binding antibody concentrations ($\log_{10}$-scale) by percent of participants with antibody concentrations at baseline and each post-baseline visit time point.
- Data listing.

To evaluate the potential impact of delayed (ie, outside the widened window due to COVID-19 pandemic) Dose 2 vaccination on the immune response, the following additional outputs will be generated (only if more than 10% of participants in the immunogenicity subset receive delayed [ie, outside the -3/+28 days window around Day 57] Dose 2 vaccination) for the binding antibody concentrations and presented for participants having received Dose 2 vaccination within the -3/+28 days window around the Day 57 visit (as defined in CTP Amendment 3[1]) window versus those having received Dose 2 outside that window:

- Table of summary statistics (including geometric means and corresponding 95% CIs, geometric mean fold increase [from Pre-dose 1 and Pre-dose 2] with corresponding 95% CI), responder rates and positive sample interpretation (ie, showing number, percentage and the exact 95% Clopper-Pearson CI) at all available time points.
- Dot plots (on a $\log_{10}$-scale) with distinction between positive and negative sample interpretations at all available time points.
- Scatter plot of the 21 days post Dose 2 immune response versus the elapsed time (days) between Doses 1 and 2 vaccinations.

6.3.2. Immunogenicity Against the Vector

For the booster cohort, the following will be defined for Ad26 VNA titers (IC_{90} titers):

Sample interpretation: a sample will be considered positive, if the value is above the assay-specific LLOQ.

The following outputs will be generated and presented by vaccination groups (ie, only Groups 5 and 6):

- Table of summary statistics (including geometric means and 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) of binding antibody responses (EU/mL) against Ad26 VNA (IC_{90} titers) at various time points (with Spearman's correlation coefficients).
- Data listing.

REFERENCES

1. VAC52150EBL3004 Protocol Amendment 3: 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. (15 June 2020).
2. FDA guidance on the conduct of clinical trials during the COVID-19 pandemic. Available at: https://www.fda.gov/media/136238/download. Accessed June 2020.
3. EMA guidance on the conduct of clinical trials during the COVID-19 pandemic. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf. Accessed June 2020.

ATTACHMENTS

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 of the CTP[1].

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.

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 (ie, 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 (ie, 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.