

## SYNOPSIS

<u>Name of Sponsor/Company</u>	Janssen Vaccines & Prevention B.V.*
<u>Name of Investigational Product</u>	VAC52150 (Ad26.ZEBOV, MVA-BN-Filo [MVA-mBN226B])

\* Janssen Vaccines & Prevention B.V. (formerly known as Crucell Holland B.V.) is a Janssen pharmaceutical company of Johnson & Johnson and is hereafter referred to as the sponsor of the study.

**Status:** Approved

**Date:** 2 October 2019

**Protocol No.:** VAC52150EBL2002

**Title of Study:** A Randomized, Observer-blind, Placebo-controlled, Phase 2 Study to Evaluate the Safety, Tolerability and Immunogenicity of Different Prime-boost Regimens of the Candidate Prophylactic Vaccines for Ebola Ad26.ZEBOV and MVA-BN-Filo in Healthy Adults, Including Elderly Subjects, HIV-infected Subjects, and Healthy Children in Two Age Strata in Africa

**NCT No.:** NCT02564523

**Clinical Registry No.:** CR107249

**Principal Investigator:** Barry Houreratou, MD - Le Centre MURAZ, PPD, Burkina Faso

**Study Center(s):** The study was conducted in 4 countries in Africa: Burkina Faso (2 sites), Cote d'Ivoire (2 sites), Kenya (1 site), and Uganda (2 sites).

**Publication (Reference):** Not applicable

**Study Period:** 09 November 2015 (date first participant signed informed consent) to 12 February 2019 (date of last observation for last participant recorded as part of the database).

**Phase of Development:** 2

### Objectives:

The primary objective of the study was:

- To assess the safety and tolerability of different vaccination schedules of Ad26.ZEBOV and MVA-BN-Filo administered intramuscularly (IM) as 2-dose heterologous regimens on Days 1 and 29, Days 1 and 57 or Days 1 and 85 in human immunodeficiency virus (HIV)-uninfected adults, including elderly, and Days 1 and 29 or Days 1 and 57 in HIV-infected adults and HIV-uninfected children in 2 age strata.

The secondary objectives of the study were:

- To assess humoral immune responses to Ebola virus glycoprotein (EBOV GP), as measured by Filovirus Animal Nonclinical Group enzyme-linked immunosorbent assay (EBOV GP FANG ELISA) at 21 days post dose 2, of different vaccination schedules of Ad26.ZEBOV and MVA-BN-Filo administered IM as 2-dose heterologous regimens on Days 1 and 29, Days 1 and 57 or Days 1 and 85 in HIV-uninfected adults, including elderly, and Days 1 and 29 or Days 1 and 57 in HIV-infected adults and HIV-uninfected children in 2 age strata.
- To assess the safety and tolerability of a booster vaccination with Ad26.ZEBOV (or placebo) administered IM at least 1 year after dose 1 in a subset of approximately 90 HIV-uninfected adults, including elderly.

The exploratory objectives of the study were:

- To assess humoral immune responses to EBOV GP, measured by EBOV GP FANG ELISA, at other timepoints of the different vaccination schedules of Ad26.ZEBOV and MVA-BN-Filo administered IM as 2-dose heterologous regimens on Days 1 and 29, Days 1 and 57 or Days 1 and 85, in HIV-uninfected adults, including elderly, and Days 1 and 29 or Days 1 and 57 in HIV-infected adults and HIV-uninfected children in 2 age strata.
- To assess the neutralizing capacity of the EBOV GP-specific humoral immune responses, as measured by a virus neutralization assay (VNA), of the different vaccination schedules of Ad26.ZEBOV and MVA-BN-Filo administered IM 2-dose heterologous regimens on Days 1 and 29, Days 1 and 57 or Days 1 and 85, in HIV-uninfected adults, including elderly, and Days 1 and 29 or Days 1 and 57 in HIV-infected adults and HIV-uninfected children in 2 age strata.
- To explore humoral and cellular immune responses to different variants of EBOV GP and the adenovirus and/or MVA vector backbone of the various vaccination schedules tested.
- To explore humoral and cellular immune responses to filovirus GPs and/or Tai Forest virus nucleoprotein (TAFV NP), if assays are available.
- To assess humoral immune responses to EBOV GP, measured by EBOV GP FANG ELISA at various timepoints following a booster vaccination with Ad26.ZEBOV (or placebo) administered IM at least 1 year post dose 1 in approximately 90 HIV-uninfected adults, including elderly.

This report includes safety and tolerability data, as well as data on humoral immune responses to EBOV GP as measured by FANG ELISA and by an EBOV GP pseudovirion neutralization assay (psVNA), data on cellular immune responses to EBOV GP as measured by interferon gamma enzyme-linked immunospot (IFN- $\gamma$  ELISpot) assay and intracellular cytokine staining (ICS), data on humoral immune responses to Marburg virus (MARV) GP and Sudan virus (SUDV) GP as measured by MARV GP ELISA and SUDV GP ELISA, respectively, and data on humoral immune responses to the Ad26 vector backbone as measured by Ad26 neutralization assay. Other exploratory objectives have not been assessed due to unavailability of the required assays.

**Methodology:** This was a randomized, observer-blind, placebo-controlled, parallel-group, multicenter, Phase 2 clinical study in Africa to evaluate the safety, tolerability and immunogenicity of different 2-dose heterologous vaccination regimens using Ad26.ZEBOV  $5 \times 10^{10}$  viral particles (vp) as dose 1 and MVA-BN-Filo  $1 \times 10^8$  infectious units (Inf.U) as dose 2 at a 28-, 56- or 84-day interval in HIV-uninfected adult and elderly participants (Cohort 1). The same vaccination schedules, except for the 84-day interval schedule, were evaluated in HIV-infected adults (Cohort 2a) and HIV-uninfected adolescents and children (Cohort 2b and Cohort 3, respectively).

At selected sites in Cohort 1 (Groups 1 and 2; see [Figure 1](#)), a booster dose of Ad26.ZEBOV (or placebo) was administered at 1 year post dose 1 (window: +3 months) in those participants who consented to this (Cohort 1 substudy). Participants who received a delayed dose 2 vaccination or did not receive dose 2 at all (eg, due to the study pause; see '*Study Pause and Subsequent Delay in Dose 2 Vaccinations*' below) were not included in the Cohort 1 substudy.

The study planned to enroll 1,056 participants who never received a candidate Ebola vaccine and had no prior exposure to Ebola virus (including travel to epidemic Ebola areas less than 1 month prior to screening) or a diagnosis of Ebola virus disease (EVD). The study cohorts were enrolled sequentially:

- HIV-uninfected adult and elderly participants (aged 18-70 years, Cohort 1)
- HIV-infected adult participants (aged 18-50 years, Cohort 2a)
- HIV-uninfected children in 2 age strata (adolescents aged 12-17 years, Cohort 2b; and children aged 4-11 years, Cohort 3).

Within Cohort 1, participants were enrolled in parallel and randomized (1:1:1) to the 28-day, 56-day and 84-day interval schedules (Groups 1, 2 and 3, respectively) at baseline until a target of 132 participants had been included in Group 3. Afterwards, randomization in this cohort proceeded in a 1:1 ratio to Groups 1 and 2. Within Cohorts 2a, 2b and 3, participants were enrolled in parallel and randomized (1:1) to Groups 1 and 2 at baseline. Participants were randomly assigned to groups within cohorts (stratified by peripheral blood mononuclear cells [PBMC] sampling capability of the selected sites), and within groups randomly assigned to Ad26.ZEBOV and MVA-BN-Filo, or placebo, in a 5:1 ratio. In Cohort 1, participants were stratified by age: 18-50 years and >50 years. In the Cohort 1 substudy, the participants who had received the active regimen received Ad26.ZEBOV as a booster dose; those who had received the placebo regimen received placebo as a booster dose.

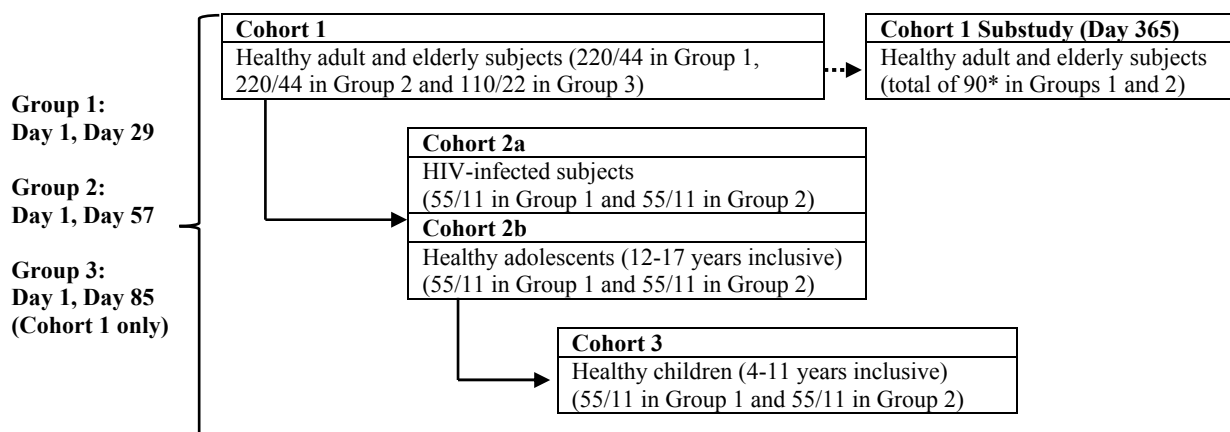
Progression to the next cohort, in an age de-escalation fashion, proceeded following a favorable review by the Independent Data Monitoring Committee (IDMC) commissioned for this study:

- Cohorts 2a and 2b started when 25% of participants in Cohort 1 had completed the 7-day post-dose 1 visit, and
- Cohort 3 started when 50% of participants in Cohort 2b had completed the 7-day post-dose 1 visit.

The real-time monitoring of the blinded data was conducted by the sponsor. The interim data (unblinded) were provided to and reviewed by the IDMC. The decision to open Cohorts 2a, 2b and 3 for enrollment was based on the sponsor's (blinded) and IDMC's (unblinded) review of the interim safety data.

A schematic overview of the study design is presented in [Figure 1](#).

**Figure 1: Schematic Overview of the Study**



N/n: planned number of subjects per group to be randomized to Ad26.ZEBOV, MVA-BN-Filo regimen/placebo regimen.

- Cohorts 2a and 2b: started when 25% of subjects from Cohort 1 had reached the 7-day post-dose 1 visit.
- Cohort 3: started when 50% of subjects from Cohort 2b had reached the 7-day post-dose 1 visit.
- \* Subjects who received Ad26.ZEBOV and MVA-BN-Filo, received Ad26.ZEBOV as a booster dose 1 year post dose 1 (window: +3 months). Subjects who received placebo, received placebo as a booster dose 1 year post dose 1 (window: +3 months).

The study included a screening phase of up to 8 weeks (starting from the moment the participant signed the informed consent form [ICF] and/or informed assent), a vaccination phase in which participants received dose 1 at baseline (Day 1) followed by dose 2 on Day 29, 57 or 85, a post-vaccination phase until 42 days post dose 2, and a long-term follow-up phase until Day 365. The Cohort 1 substudy included a vaccination phase in which participants received a booster dose at 1 year post dose 1 (window: +3 months), a post-vaccination phase until 21 days post booster, and a long-term follow-up phase until 1 year post booster.

Participants who completed the 6-month post-dose 1 visit (which was replaced with the 6-month post-dose 2 visit per Amendment 2) and/or Day 365 visit prior to the approval of Amendment 2 were required to attend the 6-month post-dose 2 visit and Day 365 visit after the approval of Amendment 2. Participants were considered to have completed the study if they had completed all assessments at the 6-month post-dose 2 visit or Day 365 visit (1 year post booster dose in Cohort 1 substudy), whichever occurred later.

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

- Ad26.ZEBOV ( $5 \times 10^{10}$  vp) on Day 1, followed by MVA-BN-Filo ( $1 \times 10^8$  Inf.U) on Days 29, 57 or 85;  
*or*
- Placebo (0.9% saline) on Day 1, followed by a second dose of placebo on Days 29, 57 or 85.

In the Cohort 1 substudy, approximately 90 HIV-uninfected adults from Groups 1 and 2 were to receive a booster dose with Ad26.ZEBOV  $5 \times 10^{10}$  vp or placebo at 1 year post dose 1 (window: +3 months).

Within each cohort, study-site personnel (except for those with primary responsibility for study vaccine preparation and dispensing) were blinded to study vaccine allocation until the last participant in that cohort had completed the study. Investigators and participants were blinded to study vaccine allocation until the final analysis (for Cohorts 1, 2a, and 2b) or formal interim analysis (Cohort 1 substudy and Cohort 3). Sponsor personnel were blinded to study vaccine allocation until the last participant in that cohort had completed the 6-month post-dose 2 visit or discontinued earlier.

The investigators and sponsor's medical monitor were responsible for the safety monitoring of the study. They reviewed the safety of participants on an ongoing basis and the sponsor's medical monitor was involved in all discussions and decisions. None of the prespecified pausing rules described in the protocol was met during this study.

#### Study Pause and Subsequent Delay in Dose 2 Vaccinations

On 28 April 2016, the sites were notified to halt all vaccinations due to the occurrence of Miller Fisher syndrome in a study participant in the Phase 2 study VAC52150EBL2001. This serious adverse event was initially considered to be possibly related to study vaccine by the investigator. After extensive evaluation, the event was considered to be doubtfully related to the study vaccine and most likely related to a prior upper respiratory tract infection by the investigator and the sponsor. Per sponsor decision, all vaccinations were to be halted until the safety language of the ICF was updated and approved.

On 19 May 2016, when the above study pause was still in effect, a second serious adverse event report was received in the Phase 2 study VAC52150EBL2001 (possible cervical myelitis, later reported as small fiber neuropathy). This event also was assessed as possibly related to study vaccine by the investigator and evaluated further. The initial report of 'possible cervical myelitis' triggered a clinical hold issued by the Food and Drug Administration (FDA) on 26 May 2016 for all clinical studies of Ad26.ZEBOV and MVA-BN-Filo ongoing at that time. After the receipt of follow-up information, on 16 June 2016, the FDA lifted the hold.

The interruption in dosing affected more than 200 participants in Cohort 1 of the present study (VAC52150EBL2002), of whom some were awaiting dose 1 and some were awaiting dose 2. When approval was granted by the Ethics Committees and Health Authorities, a late dose 2 vaccination was offered to those participants who were out-of-window for dose 2.

Participants who were awaiting dose 1 and whose screening period was longer than the protocol-defined 8 weeks as a result of the pause, were allowed to be rescreened once. These participants had to sign a new ICF and undergo new safety laboratory testing, vital signs measurements, ECG recording, and physical examination within 28 days of dose 1 vaccination. After screening, these participants followed the same procedures as those unaffected by the study pause.

Participants who were outside of the protocol-defined dose 2 vaccination window due to the pause could choose to receive a late dose 2 upon approval by the Ethics Committees and Health Authorities per site regulations. These participants had to sign a new ICF. Participants who agreed to the late dose 2 followed the same post-dose 2 procedures as participants whose dose 2 vaccination was unaffected by the study pause.

Participants who had received dose 1 but were not willing or allowed to receive a late dose 2 needed to sign a new ICF to allow for quarterly safety follow-ups. All post-dose 1 visits were performed despite the interruption in dosing. After the 7-day post-dose 1 and 14-day post-dose 1 visits (only in Groups 2 and 3 of Cohort 1), these participants were followed every 3 months after dose 1 for safety evaluations only (and immunogenicity at the 6-month and 1-year post-dose 1 visits), until Day 365. Information at these timepoints (except for the 6-month and the 1-year post-dose 1 visits) could be collected by telephone contact, visit to the site or by a home visit, according to local practice.

**Number of Participants (planned and analyzed):** A total of 1,056 participants were planned to be enrolled in the study: 660 in Cohort 1 and 132 each in Cohort 2a, Cohort 2b, and Cohort 3 (see also [Figure 1](#) above). The numbers of participants that were analyzed are shown for each cohort in [Table 1](#). A subset of 90 participants received a booster dose in the Cohort 1 substudy (73 Ad26, 17 placebo).

**Table 1: Number of Subjects (Planned and Analyzed)**

	Cohort 1 (Healthy Adults and Elderly) 18-70 Years		Cohort 2a (HIV-infected Adults) 18-50 Years		Cohort 2b (Adolescents) 12-17 Years		Cohort 3 (Children) 4-11 Years	
	Ad26, MVA (, Ad26)	Placebo, Placebo (, Placebo)	Ad26, MVA	Placebo, Placebo	Ad26, MVA	Placebo, Placebo	Ad26, MVA	Placebo, Placebo
Planned	550	110	110	22	110	22	110	22
FA Set	559 <sup>a</sup>	109 <sup>a</sup>	118	24	110	21	108	24
PP Analysis Set	337	63	117	23	107	20	107	23
IG Analysis Set	527	101	117	24	109	20	108	23

FA: Full Analysis; PP: Per Protocol; IG: Immunogenicity

For the definitions of the analysis sets, refer to 'Statistical Methods' below.

<sup>a</sup> A subset of 90 subjects received a booster dose in the Cohort 1 substudy (73 Ad26, 17 placebo).

**Main Criteria for Inclusion:** Screening was performed within 8 weeks of dose 1 vaccination. In Cohort 1, HIV-uninfected participants were healthy (per investigator's clinical judgment based on medical history, ECG, physical examination, vital signs assessments, as well as clinical laboratory testing) and between 18 and 70 years of age (inclusive) at time of randomization. In Cohort 2a, participants had to be between 18 and 50 years of age (inclusive) at time of randomization, had to have documented HIV infection for at least 6 months prior to screening and a screening CD4+ cell count >350 cells/μL, be on stable regimen of highly active anti-retroviral therapy (HAART) fulfilling protocol-specific criteria, and be in an otherwise reasonably good medical condition (absence of AIDS-defining illness or clinically significant disease) in the investigator's clinical judgment based on medical history, ECG, physical examination, vital signs assessments, as well as clinical laboratory testing. Cohorts 2b and 3 enrolled participants whose age on the day of randomization was within one of 2 age strata: 12 to 17 years or 4 to 11 years (all ages inclusive). Participants had to be healthy per investigator's clinical judgment (and the parent[s]/legal guardian) on the basis of medical history, physical examination and vital signs assessments, as well as clinical laboratory testing. Participants diagnosed with EVD, or those with prior exposure to Ebola virus (including travel to an epidemic Ebola area within 1 month before screening), and participants who had received a candidate Ebola vaccine or any experimental candidate Ad26- or MVA-based vaccine in the past, or with a known allergy or a history of anaphylaxis or other serious adverse reactions to vaccines or to vaccine products, were excluded from all cohorts (1, 2a, 2b, 3).

**Test Product, Dose and Mode of Administration, Batch No.:** Ad26.ZEBOV, 5x10<sup>10</sup> vp (concentration of 1x10<sup>11</sup> vp/mL), 0.5 mL IM injection (Batch No. 0000032645 and 0000032642); and MVA-BN-Filo,

$1 \times 10^8$  Inf.U (concentration of  $2 \times 10^8$  Inf.U/mL), 0.5 mL IM injection (Batch No. 0000032792 and 0000032790).

**Reference Therapy, Dose and Mode of Administration, Batch No.:** 0.9% saline (placebo), 0.5 mL IM injection (406501).

**Duration of Treatment:** 2-dose heterologous vaccination regimens administered at a 28-day, 56-day or 84-day interval in Cohort 1 (in a subset of participants in the 28-day or 56-day interval schedule followed by a booster dose at 1 year post dose 1); and 2-dose heterologous vaccination regimens administered at a 28-day or 56-day interval in Cohorts 2a, 2b and 3.

### Criteria for Evaluation:

Safety Evaluations: Safety was assessed in all participants through collection of solicited local and solicited systemic adverse events (reactogenicity), unsolicited adverse events, immediate reportable events (IREs)\*, and serious adverse events. Participants were closely observed by study-site personnel for a total of 60 ( $\pm 15$ ) minutes after dose 1 and dose 2, or for a total of 30 ( $\pm 10$ ) minutes after the booster dose or longer if deemed necessary by the investigator (eg, in case of grade 3 adverse events), and any unsolicited and solicited local and solicited systemic adverse events were documented during this period. Upon discharge from the site, all participants received a diary, a thermometer and a ruler to measure solicited local reactions and body temperature. Participants were instructed to record solicited local and systemic adverse events in the diary in the evening after each study vaccination and then daily for the next 7 days at about the same time each day. For the collection of solicited systemic adverse events, a different diary card was used in Cohorts 1, 2a, 2b versus Cohort 3. Cohorts 1, 2a and 2b collected nausea, fatigue, headache, myalgia, arthralgia, chills and pyrexia, while in Cohort 3, decreased activity, decreased appetite, irritability, vomiting, and pyrexia were collected.

The investigator documented unsolicited adverse events from signing of the ICF or assent form onwards until 42 days post-last vaccination (excluding the booster dose), and again from the day of the booster dose until 28 days thereafter in the Cohort 1 substudy. Serious adverse events and IREs were documented from signing of the ICF or assent form onwards until end of study. Other safety assessments included vital signs, clinical laboratory testing, ECG (only in participants aged  $\geq 18$  years), physical examinations, and pregnancy testing.

The toxicity grading scale used for the severity grading of adverse events was adapted from the Division of Microbiology and Infectious Diseases (DMID) Toxicity Tables, including DMID tables for use in trials enrolling healthy adults and DMID tables for use in trials enrolling children greater than 3 months of age. For adverse events not included in the tables, the severity criteria outlined in the protocol were used.

The toxicity scales used for assessments of clinical laboratory values were based on the FDA toxicity grading scale for healthy adults and adolescents enrolled in preventive vaccine trials and DMID toxicity tables for use in trials enrolling children greater than 3 months of age.

Immunogenicity Evaluations: Sample collection and processing was performed by the site staff according to current versions of approved standard operating procedures (SOPs). The immunogenicity assessments included in the analysis described in this report are summarized in [Table 2](#).

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\* The following neuroinflammatory disorders were categorized as immediate reportable events:

Cranial nerve disorders, including paralyses/paresis (eg, Bell's palsy); optic neuritis; multiple sclerosis; transverse myelitis; Guillain-Barré syndrome, including Miller Fisher syndrome, Bickerstaff's encephalitis and other variants; acute disseminated encephalomyelitis, including site-specific variants (eg, non-infectious encephalitis, encephalomyelitis, myeloradiculomyelitis, myelitis); myasthenia gravis and Lambert-Eaton myasthenic syndrome; immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy); narcolepsy; isolated paresthesia of more than 7 days duration.



**Table 2: Immunogenicity Assessments Included in the Analysis Described in This Report**

Sample	Immunogenicity Assessment	Assay
Serum	EBOV GP-specific binding antibody levels	FANG ELISA (ELISA units/mL)
	EBOV GP-specific neutralizing antibody levels	psVNA (IC <sub>50</sub> titer) <sup>a</sup>
	MARV GP-specific binding antibody levels	MARV GP ELISA (ELISA units/mL) <sup>a</sup>
	SUDV GP-specific binding antibody levels	SUDV GP ELISA (ELISA units/mL) <sup>a</sup>
	Neutralizing antibody levels against the Ad26 vector backbone	Ad26 VNA (IC <sub>90</sub> titer)
PBMC, at selected sites <sup>b</sup>	IFN- $\gamma$ producing T cell responses to EBOV GP	IFN- $\gamma$ ELISpot (SFU/10 <sup>6</sup> PBMC)
	T-cell responses to EBOV GP (including IFN- $\gamma$ and/or IL-2 and/or TNF- $\alpha$ producing CD4+/CD8+ T-cells)	ICS (% of subset)

EBOV GP: Ebola virus glycoprotein; ELISpot: enzyme-linked immunospot; FANG ELISA: Filovirus Animal Nonclinical Group enzyme-linked immunosorbent assay; ICS: intracellular cytokine staining; IC<sub>50/90</sub>: 50%/90% inhibitory concentration; IFN: interferon; IL: interleukin; MARV: Marburg virus; psVNA: pseudovirion neutralization assay; SFU/10<sup>6</sup> PBMC: spot-forming units per million peripheral blood mononuclear cells; SUDV: Sudan virus; TNF: tumor necrosis factor; VNA: virus neutralization assay

<sup>a</sup> This report includes psVNA, MARV GP ELISA and SUDV GP ELISA data for a subset of Cohort 1 participants at selected timepoints.

<sup>b</sup> Target: 165 participants [138 Ad26, MVA and 27 placebo] in Cohort 1 and 33 participants [28 Ad26, MVA and 5 placebo in each of the other cohorts). PBMC samples were optional for participants in the Cohort 1 substudy and were only collected in a subset of participants.

In the present study, psVNA, IFN- $\gamma$  ELISpot and ICS were not assessed for the 84-day interval schedule since this is not the proposed vaccine regimen intended for regulatory approval.

### Statistical Methods:

**Sample Size Determination:** The overall planned sample size of N=1,056 included 880 participants who were to receive the 2-dose vaccination regimen consisting of Ad26.ZEBOV and MVA-BN-Filo, in order to substantially contribute to the overall safety database of the regimen.

**Analysis Sets:** The following analysis sets were used in the analysis described in this report:

- **Full Analysis Set:** all participants who were randomized and received at least one dose of study vaccine (Ad26.ZEBOV, MVA-BN-Filo or placebo), regardless of the occurrence of protocol deviations.
- **Per Protocol Analysis Set:** all randomized and vaccinated participants, who received both dose 1 and dose 2 (administered within the protocol-defined window), had at least one post-vaccination (ie, after the date of vaccination) evaluable immunogenicity sample, and had no major protocol deviations (also referred to as major protocol violations) influencing the immune response.

For the Cohort 1 substudy: all participants in the Per Protocol Set as described above, who received the booster, had at least one post-booster (ie, after the date of vaccination) evaluable immunogenicity sample, and no major protocol deviations influencing the immune response.

- **Immunogenicity Analysis Set:** all randomized and vaccinated participants who had at least one post-vaccination (ie, after the date of vaccination) evaluable immunogenicity sample.

**Safety:** Summaries of adverse events and of other safety data were based on the Full Analysis Set.

The analysis of unsolicited adverse events was based on all participants included in the Full Analysis Set; the analysis of solicited adverse events (also referred to as reactogenicity) was based on participants in the Full Analysis Set with reactogenicity assessments available in the database.

No formal statistical testing of safety data was planned or performed.

A sensitivity analysis was performed on Cohort 1 to investigate the impact of delayed dose 2 vaccinations on the safety and tolerability profiles. For this analysis, participants were categorized based on the actual time interval between dose 1 and dose 2 (see [Table 4](#) below).

Adverse events and clinical laboratory analyte values were summarized descriptively and listed. Physical examination and ECG findings were only listed. For Cohorts 1, 2a and 2b, a listing of participants with vital sign abnormalities, including toxicity grades, was provided for the planned assessments at screening and prior to each vaccination. For Cohort 3, no toxicity grading table was available for vital signs; data in this cohort were summarized descriptively and listed for the planned assessments at screening, prior to each vaccination, and at 7 days after each vaccination.

**Immunogenicity:** The primary immunogenicity analysis was done on the Per Protocol Analysis Set. For Cohort 1, the analysis was repeated on the Immunogenicity Analysis Set.

No formal statistical testing of immune response data was planned or performed.

Summary statistics for observed values and changes from reference timepoints were calculated for each timepoint. Positive sample interpretation and the responder rates (per definitions as provided in [Table 3](#)) were summarized, showing frequency, percentage and the exact 95% Clopper-Pearson confidence interval (CI) for each timepoint.

A correlation plot between EBOV GP-specific binding antibody concentrations (ELISA) and EBOV GP-specific neutralizing antibody titers (psVNA) was prepared, including Spearman correlation coefficients. Correlation plots between EBOV and MARV GP, between EBOV and SUDV GP, and between MARV and SUDV GP-specific binding antibody concentrations were also prepared, as well as cross-tabulations showing the numbers and percentages of participants with positive samples and responses to combinations of GPs (ie, EBOV and MARV GPs, EBOV and SUDV GPs, MARV and SUDV GPs, and EBOV, MARV and SUDV GPs).

**Table 3: Responder Definitions**

EBOV GP FANG ELISA	Sample interpretation was negative at baseline and positive post baseline and the post-baseline value was greater than 2.5x LLOQ, or sample interpretation was positive both at baseline and post baseline and there was a greater than 2.5-fold increase from baseline. [LLOQ=36.11 ELISA units/mL]
EBOV GP psVNA	Sample interpretation was negative at baseline and positive post baseline and the post-baseline value was greater than 2x LLOQ, or sample interpretation was positive both at baseline and post baseline and there was a greater than 2-fold increase from baseline. [LLOQ=120 IC <sub>50</sub> titer]
EBOV GP IFN- $\gamma$ ELISpot	Sample interpretation was negative at baseline and positive post baseline and the post-baseline value was greater than 2x the threshold, or if the sample interpretation was positive both at baseline and post baseline and there was a greater than 2-fold increase from baseline. [Threshold=50 SFU/10 <sup>6</sup> PBMC]
EBOV GP ICS	Sample interpretation was negative at baseline and positive post baseline and the post-baseline value was greater than 2x LLOQ, or sample interpretation was positive both at baseline and post baseline and there was a greater than 2-fold increase from baseline in background-adjusted percentage of the combined peptide pools. [LLOQ=0.04%]
MARV GP and SUDV GP ELISA	Sample interpretation was negative at baseline and positive post-baseline, or sample interpretation was positive at both timepoints and there was a >3-fold increase from baseline. [LLOQ for MARV GP ELISA=19.19 ELISA units/mL, and LLOQ for SUDV GP ELISA=14.86 ELISA units/mL]

A sensitivity analysis was performed on Cohort 1 to evaluate the impact of delayed dose 2 vaccinations on EBOV GP-specific binding antibody responses (ELISA). For this analysis, participants were categorized according to the actual time interval between dose 1 and dose 2 as shown in [Table 4](#) below.



**Table 4: Vaccination Schedules for Sensitivity Analysis on Cohort 1 to Evaluate Impact of a Delayed Dose 2**

Group	Group Label (Ad26.ZEBOV, MVA-BN-Filo)	Window (Days)
A	28-day interval between dose 1 and dose 2	[14; 42]
B	56-day interval between dose 1 and dose 2	[43; 70]
C	84-day interval between dose 1 and dose 2	[71; 98]
D	140-day interval between dose 1 and dose 2	[99; 168]
E	196-day interval between dose 1 and dose 2	[169; 224]
F	252-day interval between dose 1 and dose 2	[225; 279]
G	≥280-day interval between dose 1 and dose 2	≥280

Note: The day of the dose 1 vaccination was Day 1.

Some participants in the Cohort 1 substudy received the booster dose within 30 days after Day 365 (post dose 1) whereas others received it beyond 30 days after Day 365 (post dose 1). A sensitivity analysis was performed on the EBOV GP-specific binding antibody responses (ELISA) to evaluate the robustness of receiving the booster dose within 30 days after Day 365 (post dose 1) contrasted with receiving the booster dose beyond 30 days after Day 365 (post dose 1).

### Post-hoc Analyses

Because sample positivity for EBOV GP-specific binding antibodies was observed at baseline, post hoc analyses were performed to determine if there was a relationship between a positive baseline ELISA value and subsequent immune response. Summary statistics were calculated for EBOV GP-specific binding antibody responses at available timepoints, stratified by baseline ELISA concentration categories (<lower limit of quantification [LLOQ], LLOQ-100 ELISA units/mL, >100-1000 ELISA units/mL, >1000 ELISA units/mL). Correlation plots between the baseline EBOV GP-specific binding antibody concentrations and selected post-baseline timepoints were also prepared, including Spearman correlation coefficients.

Correlation plots between pre-vaccination Ad26 neutralizing antibody titers (Ad26 VNA) and EBOV GP-specific binding antibody levels (ELISA) were also prepared, including Spearman correlation coefficients.

## RESULTS:

### STUDY POPULATION:

In total, 1,073 participants were randomized and received at least one dose of study vaccine. The numbers of participants are summarized by cohort and vaccination schedule in [Table 5](#).

**Table 5: Subject Disposition: Subjects Who Received at Least One Dose of Study Vaccine**

	Cohort 1 (Healthy Adults and Elderly) 18-70 Years		Cohort 2a (HIV-infected Adults) 18-50 Years		Cohort 2b (Adolescents) 12-17 Years		Cohort 3 (Children) 4-11 Years	
	Ad26, MVA (, Ad26)	Placebo, Placebo (, Placebo)	Ad26, MVA	Placebo, Placebo	Ad26, MVA	Placebo, Placebo	Ad26, MVA	Placebo, Placebo
Group 1: 28-day interval	225 (34) <sup>a</sup>	43 (8) <sup>a</sup>	59	12	55	11	54	12
Group 2: 56-day interval	224 (39) <sup>a</sup>	44 (9) <sup>a</sup>	59	12	55	10	54	12
Group 3: 84-day interval	110	22	-	-	-	-	-	-

<sup>a</sup> Per protocol, only a subset of subjects in Groups 1 and 2 of Cohort 1 received a booster dose (Cohort 1 substudy).

More than 95% of the participants completed the study ([Table 6](#)).

**Table 6: Subject Disposition: Study Completion and Termination**

	Cohort 1 (Healthy Adults and Elderly) 18-70 Years	Cohort 2a (HIV-infected Adults) 18-50 Years	Cohort 2b (Adolescents) 12-17 Years	Cohort 3 (Children) 4-11 Years
Full Analysis Set	668	142	131	132
Completed	640 (95.8%)	139 (97.9%)	125 (95.4%)	131 (99.2%)
Discontinued	28 (4.2%)	3 (2.1%)	6 (4.6%)	1 (0.8%)

In Cohort 1, the most common reasons for early study discontinuation were protocol deviations (reported in 10 [1.5%] participants) and loss to follow-up (8 [1.2%] participants). The 10 discontinuations because of protocol deviations were due to donation of blood within the prohibited timeframe (in 7 participants) and expiry of the calibrations of pharmacy thermometers used to monitor stored study vaccine at the site (in 3 participants) (no participants received damaged vaccine). There were no study discontinuations in Cohort 1 due to adverse events. In total, 52 (7.8%) participants in Cohort 1 did not receive dose 2, and 207 (31.0%) participants received dose 2 outside of the protocol-defined interval (ie, up to 483 days post dose 1), mainly due to the study pause. No discontinuations from vaccination in Cohort 1 due to adverse events were reported.

In Cohort 2a, the reasons for study discontinuation were loss to follow-up, withdrawal by the participant, and death (due to alcohol poisoning) (1 [0.7%] participant each). One participant in Cohort 2a did not receive the dose 2 vaccination due to pregnancy; there were no discontinuations from study vaccination due to adverse events.

In Cohorts 2b and 3, the most common reasons for study discontinuation were loss to follow-up and withdrawal by the parent/legal guardian (2 [0.8%] participants each). One participant in Cohort 2b did not complete the study as the participant died of typhoid fever and malaria with onset on Day 52 post dose 2 (MVA-BN-Filo), and 1 participant in Cohort 3 did not complete the study due to a serious adverse event (second-degree burns due to a domestic accident, post placebo). The participant with second-degree burns did not receive the dose 2 vaccination. No other discontinuations from vaccination due to adverse events were reported in Cohorts 2b and 3. The adverse events of typhoid fever and malaria, and second-degree burns were considered to be unrelated to study vaccine by the investigator.

### ***Demographics and Baseline Characteristics***

Key demographics and baseline characteristics are summarized in [Table 7](#) for the Full Analysis Set.

Within each cohort, demographics and baseline characteristics were well balanced among groups (active and placebo) (data not shown in this Synopsis).

**Table 7: Summary of Demographics and Baseline Characteristics; Full Analysis Set**

	Cohort 1 (Healthy Adults and Elderly) 18-70 Years	Cohort 2a (HIV-infected Adults) 18-50 Years	Cohort 2b (Adolescents) 12-17 Years	Cohort 3 (Children) 4-11 Years
Analysis set: Full analysis set	668	142	131	132
Age (years) at screening				
Median	29.0	39.0	14.0	7.0
Min; Max	(18; 69)	(18; 50)	(11; 17)	(4; 11)
Body mass index (kg/m <sup>2</sup> )				
Median	22.20	23.35	18.6	--
Min; Max	(16.8; 46.1)	(15.8; 36.5)	(13.3; 33.3)	--
Weight-for-age percentile				
Median	--	--	--	24.75
Min; Max	--	--	--	(0.29; 98.26)
Sex				
Female	210 (31.4%)	99 (69.7%)	60 (45.8%)	65 (49.2%)
Male	458 (68.6%)	43 (30.3%)	71 (54.2%)	67 (50.8%)
Race				
Asian	4 (0.6%)	0	0	0
Black or African American	663 (99.3%)	142 (100.0%)	131 (100%)	132 (100%)
White	1 (0.1%)	0	0	0

Min: minimum; Max: maximum

**SAFETY RESULTS:**

This section describes the safety results by study cohort (1, 2a, 2b, and 3), summarizing data post dose 1, post dose 2, and post booster dose (in the tables referred to as Post-dose 3) separately; and data combined for the regimen (in the tables referred to as Post-dose 1 and Post-dose 2 Combined).

Post-dose 3 in the tables only applies to participants in the Cohort 1 substudy who received the booster dose; and Post-dose 1 and Post-dose 2 Combined includes data from participants who received both dose 1 and dose 2, as well as participants who only received dose 1.

***Solicited Adverse Events***

The numbers and percentages of participants with solicited adverse events are summarized by vaccination schedule in [Table 8](#) (Cohort 1), [Table 9](#) (Cohort 2a), and [Table 10](#) (Cohorts 2b and 3). In addition to the data by numbers of participants presented in the tables, results by number of doses administered are also presented for each post-dose period separately (post dose 1, post dose 2, and post dose 3); the descriptive summary that follows here provides results for each study vaccine by the overall numbers of doses administered of that vaccine during the study.

***HIV-uninfected Adult and Elderly Participants (Cohort 1) (Table 8)***

- The percentage of participants who experienced at least one solicited local adverse event was 68.4% among active vaccine recipients and 44.2% among placebo recipients in the 28-day interval schedule, 69.2% among active vaccine recipients and 52.3% among placebo recipients in the 56-day interval schedule, and 73.6% among active vaccine recipients and 54.5% among placebo recipients in the 84-day interval schedule.
- Solicited local events were observed in 54.0% of Ad26.ZEBOV doses, 57.3% of MVA-BN-Filo doses, and 37.8% of placebo doses. In the 56-day interval schedule (but not the 28-day interval schedule), the percentage of participants with at least one solicited local adverse event tended to be lower with the Ad26.ZEBOV booster dose than with the first dose of Ad26.ZEBOV.
- The most frequently observed solicited local adverse event was injection site pain.
- Grade 3 solicited local adverse events were observed in 0.3% (2/632) of Ad26.ZEBOV doses, 0.8% (4/517) of MVA-BN-Filo doses, and 0% (0/225) of placebo doses.
- The percentage of participants who experienced at least one solicited systemic adverse event was 73.3% among active vaccine recipients and 67.4% among placebo recipients in the 28-day interval schedule, 76.3% among active vaccine recipients and 63.6% among placebo recipients in the 56-day interval schedule, and 81.8% among active vaccine recipients and 77.3% among placebo recipients in the 84-day interval schedule.
- Solicited systemic adverse events were observed in 62.7% of Ad26.ZEBOV doses, 59.2% of MVA-BN-Filo doses, and 54.2% of placebo doses. In both the 28-day and 56-day interval schedule, the percentage of participants with at least one solicited systemic adverse event tended to be lower with the Ad26.ZEBOV booster dose than with the first dose of Ad26.ZEBOV.
- The 3 most frequently reported solicited systemic adverse events were fatigue, headache and myalgia.
- Grade 3 solicited systemic adverse events were observed in 2.5% (16/632) of Ad26.ZEBOV doses, 2.1% (11/517) of MVA-BN-Filo doses, and 2.2% (5/225) of placebo doses.
- Grade 3 fevers ( $>38.9^{\circ}\text{C}$ ) occurred in 0.8% (5/631) of Ad26.ZEBOV doses, 1.7% (9/517) of MVA-BN-Filo doses, and 0.4% (1/225) of placebo doses. Day of onset ranged from 1 to 8 days following vaccination and duration from 1 to 5 days. The majority (10/15 fevers) was considered to be related to study vaccine by the investigator. Of the 5 participants with grade 3 fever considered unrelated to study vaccine, one participant was diagnosed with malaria and one other participant had bronchitis.
- There was no apparent influence of the time interval between the Ad26.ZEBOV and MVA-BN-Filo doses (ie, 28, 56 or 84 days, or up to 483 days mainly due to the study pause) on the occurrence of

solicited adverse events (local or systemic) (data at the later timepoints are not tabulated in this Synopsis).

*HIV-infected Adult Participants (Cohort 2a) (Table 9)*

- The percentage of participants who experienced at least one solicited local adverse event was 67.8% among active vaccine recipients and 41.7% among placebo recipients in the 28-day interval schedule, and 67.8% among active vaccine recipients and 16.7% among placebo recipients in the 56-day interval schedule.
- Solicited local adverse events were observed in 58.5% of Ad26.ZEBOV doses, 43.6% of MVA-BN-Filo doses, and 20.8% of placebo doses.
- The most frequently observed solicited local adverse event was injection site pain.
- There were no grade 3 solicited local adverse events.
- The percentage of participants who experienced at least one solicited systemic adverse event was 83.1% among active vaccine recipients and 58.3% among placebo recipients in the 28-day interval schedule, and 67.8% among active vaccine recipients and 58.3% among placebo recipients in the 56-day interval schedule.
- Solicited systemic adverse events were observed in 67.8% of Ad26.ZEBOV doses, 49.6% of MVA-BN-Filo doses, and 39.6% of placebo doses.
- The 3 most frequent solicited systemic adverse events were fatigue, headache and myalgia.
- Grade 3 solicited systemic events were observed in 2.5% (3/118) of Ad26.ZEBOV doses, 0% (0/117) of MVA-BN-Filo doses, and 2.1% (1/48) of placebo doses. All were cases of grade 3 fever ( $>38.9^{\circ}\text{C}$ ), with an onset at 1 to 6 days post vaccination and a duration of 1 to 4 days. Three of the four grade 3 fevers were considered to be related to study vaccine by the investigator. The unrelated case was due to upper respiratory tract infection.

*Adolescents (Aged 12-17 Years) (Cohort 2b) (Table 10)*

- The percentage of participants who experienced at least one solicited local adverse event was 63.6% among active vaccine recipients and 45.5% among placebo recipients in the 28-day interval schedule, and 60.0% among active vaccine recipients and 50.0% among placebo recipients in the 56-day interval schedule.
- Solicited local adverse events were observed in 50.9% of Ad26.ZEBOV doses, 45.0% of MVA-BN-Filo doses, and 34.1% of placebo doses.
- The most frequently observed solicited local adverse event was injection site pain.
- Grade 3 solicited local adverse events were observed in 0% (0/110) of Ad26.ZEBOV doses, 0.9% (1/109) of MVA-BN-Filo doses, and 2.4% (1/41) of placebo doses.
- The percentage of participants who experienced at least one solicited systemic adverse event was 61.8% among active vaccine recipients and 36.4% among placebo recipients in the 28-day interval schedule, and 61.8% among active vaccine recipients and 60.0% among placebo recipients in the 56-day interval schedule.
- Solicited systemic adverse events were observed in 53.6% of Ad26.ZEBOV doses, 47.7% of MVA-BN-Filo doses, and 43.9% of placebo doses.
- The 3 most frequent solicited systemic adverse events were fatigue, headache and myalgia.
- Grade 3 solicited systemic events were only observed after Ad26.ZEBOV vaccination (1.8% [2/110] of doses).
- One case of fever (observed after Ad26.ZEBOV vaccination) was grade 3 in severity ( $>38.9^{\circ}\text{C}$ ). The fever started within 2 days post vaccination and resolved within 5 days. The fever was considered to be related to Ad26.ZEBOV vaccination by the investigator.

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*Children (Aged 4-11 Years) (Cohort 3) (Table 10)*

- The percentage of participants who experienced at least one solicited local adverse event was 63.0% among active vaccine recipients and 50.0% among placebo recipients in the 28-day interval schedule, and 61.1% among active vaccine recipients and 41.7% among placebo recipients in the 56-day interval schedule.
- Solicited local adverse events were observed in 50.9% of Ad26.ZEBOV doses, 40.7% of MVA-BN-Filo doses, and 31.9% of placebo doses.
- The most frequently observed solicited local adverse event was injection site pain.
- Grade 3 solicited local adverse events were only observed after Ad26.ZEBOV vaccination (2.8% [3/108] of doses).
- The percentage of participants who experienced at least one solicited systemic adverse event was 48.1% among active vaccine recipients and 25.0% among placebo recipients in the 28-day interval schedule, and 44.4% among active vaccine recipients and 41.7% among placebo recipients in the 56-day interval schedule.
- Solicited systemic events were observed in 43.5% of Ad26.ZEBOV doses, 18.5% of MVA-BN-Filo doses, and 23.4% of placebo doses.
- The most frequent solicited systemic adverse event was pyrexia. The percentage of participants with pyrexia following Ad26.ZEBOV vaccination (22.2% of doses) was higher compared to the adult and adolescent study populations (4.6% to 11.0% of doses). No such trend was observed for MVA-BN-Filo or placebo.
- Grade 3 solicited systemic events were only observed after Ad26.ZEBOV vaccination (0.9% [1/108] of doses).
- No grade 3 fevers ( $>40^{\circ}\text{C}$ ) were observed.

**Table 8: Solicited Adverse Events: Summary – Healthy Adults and Elderly; Full Analysis Set**

Subjects with at least one	Cohort 1 (Healthy Adults and Elderly)					
	28-Day Interval		56-Day Interval		84-Day Interval	
	Ad26, MVA(, Ad26)	Placebo, Placebo(, Placebo)	Ad26, MVA(, Ad26)	Placebo, Placebo(, Placebo)	Ad26, MVA	Placebo, Placebo
<b>Post-dose 1</b>	225	43	224	44	110	22
solicited AE	161 (71.6%)	30 (69.8%)	161 (71.9%)	31 (70.5%)	83 (75.5%)	15 (68.2%)
solicited AE with severity grade 3	4 (1.8%)	0	6 (2.7%)	1 (2.3%)	5 (4.5%)	1 (4.5%)
solicited local AE	123 (54.7%)	16 (37.2%)	121 (54.0%)	20 (45.5%)	63 (57.3%)	11 (50.0%)
solicited local AE with severity grade 3	0	0	1 (0.4%)	0	1 (0.9%)	0
solicited systemic AE	146 (64.9%)	27 (62.8%)	140 (62.5%)	26 (59.1%)	75 (68.2%)	14 (63.6%)
solicited systemic AE with severity grade 3	4 (1.8%)	0	6 (2.7%)	1 (2.3%)	5 (4.5%)	1 (4.5%)
solicited systemic AE considered related to vaccine	136 (60.4%)	25 (58.1%)	127 (56.7%)	23 (52.3%)	71 (64.5%)	14 (63.6%)
<b>Post-dose 2</b>	219	39	200	39	98	21
solicited AE	152 (69.4%)	15 (38.5%)	148 (74.0%)	25 (64.1%)	73 (74.5%)	15 (71.4%)
solicited AE with severity grade 3	5 (2.3%)	2 (5.1%)	2 (1.0%)	1 (2.6%)	6 (6.1%)	0
solicited local AE	126 (57.5%)	9 (23.1%)	113 (56.5%)	16 (41.0%)	57 (58.2%)	9 (42.9%)
solicited local AE with severity grade 3	2 (0.9%)	0	0	0	2 (2.0%)	0
solicited systemic AE	121 (55.3%)	14 (35.9%)	121 (60.5%)	21 (53.8%)	64 (65.3%)	14 (66.7%)
solicited systemic AE with severity grade 3	4 (1.8%)	2 (5.1%)	2 (1.0%)	1 (2.6%)	5 (5.1%)	0
solicited systemic AE considered related to vaccine	110 (50.2%)	12 (30.8%)	109 (54.5%)	16 (41.0%)	61 (62.2%)	12 (57.1%)
<b>Post-dose 1 and Post-dose 2 Combined</b>	225	43	224	44	110	22
solicited AE	185 (82.2%)	31 (72.1%)	191 (85.3%)	34 (77.3%)	95 (86.4%)	18 (81.8%)
solicited AE with severity grade 3	9 (4.0%)	2 (4.7%)	6 (2.7%)	2 (4.5%)	10 (9.1%)	1 (4.5%)
solicited local AE	154 (68.4%)	19 (44.2%)	155 (69.2%)	23 (52.3%)	81 (73.6%)	12 (54.5%)
solicited local AE with severity grade 3	2 (0.9%)	0	1 (0.4%)	0	3 (2.7%)	0
solicited systemic AE	165 (73.3%)	29 (67.4%)	171 (76.3%)	28 (63.6%)	90 (81.8%)	17 (77.3%)
solicited systemic AE with severity grade 3	8 (3.6%)	2 (4.7%)	6 (2.7%)	2 (4.5%)	9 (8.2%)	1 (4.5%)
solicited systemic AE considered related to vaccine	158 (70.2%)	28 (65.1%)	160 (71.4%)	25 (56.8%)	87 (79.1%)	16 (72.7%)
<b>Post-dose 3</b>	34	8	39	9	-	-
solicited AE	20 (58.8%)	3 (37.5%)	22 (56.4%)	4 (44.4%)	-	-
solicited AE with severity grade 3	0	0	1 (2.6%)	0	-	-
solicited local AE	18 (52.9%)	1 (12.5%)	16 (41.0%)	3 (33.3%)	-	-
solicited local AE with severity grade 3	0	0	0	0	-	-
solicited systemic AE	17 (50.0%)	2 (25.0%)	18 (46.2%)	4 (44.4%)	-	-
solicited systemic AE with severity grade 3	0	0	1 (2.6%)	0	-	-
solicited systemic AE considered related to vaccine	15 (44.1%)	2 (25.0%)	17 (43.6%)	4 (44.4%)	-	-



**Table 8: Solicited Adverse Events: Summary – Healthy Adults and Elderly; Full Analysis Set**

	Cohort 1 (Healthy Adults and Elderly)					
	28-Day Interval		56-Day Interval		84-Day Interval	
	Ad26, MVA(, Ad26)	Placebo, Placebo(, Placebo)	Ad26, MVA(, Ad26)	Placebo, Placebo(, Placebo)	Ad26, MVA	Placebo, Placebo
Subjects with at least one						

AE: adverse event

The denominator is the number of subjects with available reactogenicity data after the given dose.

Note that vaccine relates to MVA-BN-Filo, Ad26.ZEBOV or placebo.

Ad26: Ad26.ZEBOV at a dose of  $5 \times 10^{10}$  vp; MVA: MVA-BN-Filo at a dose of  $1 \times 10^8$  Inf.U.

**Table 9: Solicited Adverse Events: Summary – HIV-infected Adults; Full Analysis Set**

Subjects with at least one	Cohort 2a (HIV-infected)			
	28-Day Interval		56-Day Interval	
	Ad26, MVA	Placebo, Placebo	Ad26, MVA	Placebo, Placebo
<b>Post-dose 1</b>	59	12	59	12
solicited AE	48 (81.4%)	7 (58.3%)	45 (76.3%)	3 (25.0%)
solicited AE with severity grade 3	1 (1.7%)	0	2 (3.4%)	0
solicited local AE	34 (57.6%)	4 (33.3%)	35 (59.3%)	2 (16.7%)
solicited local AE with severity grade 3	0	0	0	0
solicited systemic AE	44 (74.6%)	7 (58.3%)	36 (61.0%)	2 (16.7%)
solicited systemic AE with severity grade 3	1 (1.7%)	0	2 (3.4%)	0
solicited systemic AE considered related to vaccine	38 (64.4%)	6 (50.0%)	33 (55.9%)	2 (16.7%)
<b>Post-dose 2</b>	58	12	59	12
solicited AE	34 (58.6%)	5 (41.7%)	31 (52.5%)	6 (50.0%)
solicited AE with severity grade 3	0	0	0	1 (8.3%)
solicited local AE	26 (44.8%)	2 (16.7%)	25 (42.4%)	2 (16.7%)
solicited local AE with severity grade 3	0	0	0	0
solicited systemic AE	32 (55.2%)	4 (33.3%)	26 (44.1%)	6 (50.0%)
solicited systemic AE with severity grade 3	0	0	0	1 (8.3%)
solicited systemic AE considered related to vaccine	28 (48.3%)	4 (33.3%)	26 (44.1%)	6 (50.0%)
<b>Post-dose 1 and Post-dose 2 Combined</b>	59	12	59	12
solicited AE	51 (86.4%)	8 (66.7%)	47 (79.7%)	7 (58.3%)
solicited AE with severity grade 3	1 (1.7%)	0	2 (3.4%)	1 (8.3%)
solicited local AE	40 (67.8%)	5 (41.7%)	40 (67.8%)	2 (16.7%)
solicited local AE with severity grade 3	0	0	0	0
solicited systemic AE	49 (83.1%)	7 (58.3%)	40 (67.8%)	7 (58.3%)
solicited systemic AE with severity grade 3	1 (1.7%)	0	2 (3.4%)	1 (8.3%)
solicited systemic AE considered related to vaccine	44 (74.6%)	7 (58.3%)	39 (66.1%)	7 (58.3%)

AE: adverse event

The denominator is the number of subjects with available reactogenicity data after the given dose.

Note that vaccine relates to MVA-BN-Filo, Ad26.ZEBOV or placebo.

Ad26: Ad26.ZEBOV at a dose of  $5 \times 10^{10}$  vp; MVA: MVA-BN-Filo at a dose of  $1 \times 10^8$  Inf.U.

**Table 10: Solicited Adverse Events: Summary – Healthy Adolescents and Children; Full Analysis Set**

	Cohort 2b (12-17 Years)				Cohort 3 (4-11 Years)			
	28-Day Interval		56-Day Interval		28-Day Interval		56-Day Interval	
	Ad26, MVA	Placebo, Placebo	Ad26, MVA	Placebo, Placebo	Ad26, MVA	Placebo, Placebo	Ad26, MVA	Placebo, Placebo
Subjects with at least one								
<b>Post-dose 1</b>	55	11	55	10	54	12	54	12
solicited AE	33 (60.0%)	4 (36.4%)	35 (63.6%)	6 (60.0%)	36 (66.7%)	6 (50.0%)	37 (68.5%)	5 (41.7%)
solicited AE with severity grade 3	1 (1.8%)	0	1 (1.8%)	0	2 (3.7%)	0	1 (1.9%)	0
solicited local AE	26 (47.3%)	3 (27.3%)	30 (54.5%)	5 (50.0%)	26 (48.1%)	6 (50.0%)	29 (53.7%)	5 (41.7%)
solicited local AE with severity grade 3	0	0	0	0	2 (3.7%)	0	1 (1.9%)	0
solicited systemic AE	29 (52.7%)	4 (36.4%)	30 (54.5%)	5 (50.0%)	24 (44.4%)	2 (16.7%)	23 (42.6%)	2 (16.7%)
solicited systemic AE with severity grade 3	1 (1.8%)	0	1 (1.8%)	0	1 (1.9%)	0	0	0
solicited systemic AE considered related to vaccine	29 (52.7%)	4 (36.4%)	30 (54.5%)	5 (50.0%)	21 (38.9%)	2 (16.7%)	20 (37.0%)	2 (16.7%)
<b>Post-dose 2</b>	55	10	54	10	54	12	54	11
solicited AE	36 (65.5%)	5 (50.0%)	27 (50.0%)	6 (60.0%)	23 (42.6%)	3 (25.0%)	26 (48.1%)	5 (45.5%)
solicited AE with severity grade 3	1 (1.8%)	0	0	1 (10.0%)	0	0	0	0
solicited local AE	29 (52.7%)	3 (30.0%)	20 (37.0%)	3 (30.0%)	22 (40.7%)	2 (16.7%)	22 (40.7%)	2 (18.2%)
solicited local AE with severity grade 3	1 (1.8%)	0	0	1 (10.0%)	0	0	0	0
solicited systemic AE	27 (49.1%)	3 (30.0%)	25 (46.3%)	6 (60.0%)	10 (18.5%)	3 (25.0%)	10 (18.5%)	4 (36.4%)
solicited systemic AE with severity grade 3	0	0	0	0	0	0	0	0
solicited systemic AE considered related to vaccine	25 (45.5%)	3 (30.0%)	25 (46.3%)	6 (60.0%)	8 (14.8%)	3 (25.0%)	7 (13.0%)	2 (18.2%)
<b>Post-dose 1 and Post-dose 2 Combined</b>	55	11	55	10	54	12	54	12
solicited AE	42 (76.4%)	6 (54.5%)	38 (69.1%)	7 (70.0%)	42 (77.8%)	7 (58.3%)	39 (72.2%)	7 (58.3%)
solicited AE with severity grade 3	2 (3.6%)	0	1 (1.8%)	1 (10.0%)	2 (3.7%)	0	1 (1.9%)	0
solicited local AE	35 (63.6%)	5 (45.5%)	33 (60.0%)	5 (50.0%)	34 (63.0%)	6 (50.0%)	33 (61.1%)	5 (41.7%)
solicited local AE with severity grade 3	1 (1.8%)	0	0	1 (10.0%)	2 (3.7%)	0	1 (1.9%)	0
solicited systemic AE	34 (61.8%)	4 (36.4%)	34 (61.8%)	6 (60.0%)	26 (48.1%)	3 (25.0%)	24 (44.4%)	5 (41.7%)
solicited systemic AE with severity grade 3	1 (1.8%)	0	1 (1.8%)	0	1 (1.9%)	0	0	0
solicited systemic AE considered related to vaccine	34 (61.8%)	4 (36.4%)	34 (61.8%)	6 (60.0%)	21 (38.9%)	3 (25.0%)	21 (38.9%)	3 (25.0%)

AE: adverse event

The denominator is the number of subjects with available reactogenicity data after the given dose.

Note that vaccine relates to MVA-BN-Filo, Ad26.ZEBOV or placebo.

Ad26: Ad26.ZEBOV at a dose of  $5 \times 10^{10}$  vp; MVA: MVA-BN-Filo at a dose of  $1 \times 10^8$  Inf.U.

### ***Unsolicited Adverse Events***

The numbers and percentages of participants who experienced unsolicited adverse events are summarized by vaccination schedule in [Table 11](#) (Cohort 1), [Table 12](#) (Cohort 2a), and [Table 13](#) (Cohorts 2b and 3). In addition to the data by numbers of participants presented in the tables, results by number of doses administered are also presented for each post-dose period separately (post dose 1, post dose 2, and post dose 3); the descriptive summary that follows here provides results for each study vaccine by the overall numbers of doses administered of that vaccine during the study. The analysis of unsolicited adverse events includes events reported up to 28 days following each vaccination.

#### *HIV-uninfected Adult and Elderly Participants (Cohort 1) (Table 11)*

- The percentage of participants with at least one unsolicited adverse event was 56.0% among active vaccine recipients and 55.8% among placebo recipients in the 28-day interval schedule, 44.6% among active vaccine recipients and 56.8% among placebo recipients in the 56-day interval schedule, and 50.9% among active vaccine recipients and 59.1% among placebo recipients in the 84-day interval schedule.
- Unsolicited adverse events were observed in 35.4% of Ad26.ZEBOV doses, 32.1% of MVA-BN-Filo doses, and 34.7% of placebo doses. In the 28-day interval schedule (but not the 56-day interval schedule), the percentage of participants with at least one unsolicited adverse event tended to be lower with the Ad26.ZEBOV booster dose than with the first dose of Ad26.ZEBOV.
- By preferred term, the most frequent unsolicited adverse events across vaccination schedules were malaria and upper respiratory tract infection. These events were reported in both active vaccine and placebo recipients, with no relevant differences between vaccines and placebo. One case of upper respiratory tract infection (post Ad26.ZEBOV vaccination) was considered to be related to study vaccine by the investigator.
- Grade 3 unsolicited adverse events were observed in 4.6% (29/632) of Ad26.ZEBOV doses, 2.9% (15/517) of MVA-BN-Filo doses, and 6.7% (15/225) of placebo doses. The majority of grade 3 events were associated with a clinical laboratory abnormality. No remarkable trends were observed.
- Related unsolicited adverse events were observed in 7.1% (45/632) of Ad26.ZEBOV doses, and 5.8% of MVA-BN-Filo and placebo doses (30/517 and 13/225, respectively). No remarkable trends were observed.
- There was no apparent influence of the time interval between the Ad26.ZEBOV and MVA-BN-Filo doses (ie, 28, 56 or 84 days, or up to 483 days mainly due to the study pause) on the occurrence of unsolicited adverse events (data at the later timepoints are not tabulated in this Synopsis).

#### *HIV-infected Adult Participants (Cohort 2a) (Table 12)*

- The percentage of participants with at least one unsolicited adverse event was 59.3% among active vaccine recipients and 75.0% among placebo recipients in the 28-day interval schedule and 55.9% among active vaccine recipients and 41.7% among placebo recipients in the 56-day interval schedule.
- Unsolicited adverse events were observed in 42.4% of Ad26.ZEBOV doses, in 37.6% of MVA-BN-Filo doses, and 37.5% of placebo doses.
- By preferred term, the most frequent unsolicited adverse events across vaccination schedules were neutropenia and upper respiratory tract infection. These events were reported in both active vaccine and placebo recipients, with no relevant differences between the vaccines and placebo. Five cases of neutropenia (1 after Ad26.ZEBOV dosing, 2 after MVA-BN-Filo dosing, and 2 after placebo dosing) were considered to be related to study vaccine by the investigator.
- Grade 3 unsolicited adverse events were observed in 7.6% (9/118) of Ad26.ZEBOV doses, 3.4% (4/117) of MVA-BN-Filo doses, and 8.3% (4/48) of placebo doses. Apart from 1 case of peptic ulcer, reported following Ad26.ZEBOV vaccination and considered to be unrelated to study vaccine by the

investigator, all grade 3 unsolicited events were associated with a clinical laboratory abnormality. No remarkable trends were observed.

- Related unsolicited adverse events were observed in 5.9% (7/118) of Ad26.ZEBOV doses, 10.3% (12/117) of MVA-BN-Filo doses, and 6.3% (3/48) of placebo doses. The majority of related events were associated with a clinical laboratory abnormality. No remarkable trends were observed.

*Adolescents (Aged 12-17 Years)(Cohort 2b) (Table 13)*

- The percentage of participants with at least one unsolicited adverse event was 63.6% among active vaccine recipients and 45.5% among placebo recipients in the 28-day interval schedule and 76.4% among active vaccine recipients and 60.0% among placebo recipients in the 56-day interval schedule.
- Unsolicited adverse events were observed in 53.6% of Ad26.ZEBOV doses, 40.4% of MVA-BN-Filo doses, and 41.5% of placebo doses.
- By preferred term, the most frequent unsolicited adverse events across vaccination schedules were malaria, upper respiratory tract infection, and hyponatremia. These 3 events were reported in active vaccine as well as placebo recipients, with no relevant differences between vaccines and placebo. None of the malaria cases and upper respiratory tract infections were considered to be related to study vaccine by the investigator; hyponatremia was considered to be related in all but 1 participant.
- Grade 3 events were observed in 10.0% (11/110) of Ad26.ZEBOV doses, 5.5% (6/109) of MVA-BN-Filo doses, and 4.9% (2/41) of placebo doses. All grade 3 events were associated with a clinical laboratory abnormality (see section on “Clinical Laboratory Abnormalities” below). No remarkable trends were observed.
- Related unsolicited events were observed in 12.7% (14/110) of Ad26.ZEBOV doses, 15.6% (17/109) of MVA-BN-Filo doses, and 9.8% (4/41) of placebo doses. Most related events were associated with a clinical laboratory abnormality. No remarkable trends were observed.

*Children (Aged 4-11 Years) (Cohort 3) (Table 13)*

- The percentage of participants with at least one unsolicited adverse event was 63.0% among active vaccine recipients and 75.0% among placebo recipients in the 28-day interval schedule and 55.6% among active vaccine recipients and 75.0% among placebo recipients in the 56-day interval schedule.
- Unsolicited adverse events were observed in 38.9% of Ad26.ZEBOV and MVA-BN-Filo doses, and in 48.9% of placebo doses.
- By preferred term, the most frequent unsolicited adverse events across vaccination schedules were malaria and rhinitis, with no relevant differences between vaccines and placebo. None of these events was considered to be related to study vaccine by the investigator.
- Grade 3 events were observed in 0.9% (1/108) of Ad26.ZEBOV doses, 1.9% (2/108) of MVA-BN-Filo doses, and 0% (0/47) of placebo doses. Apart from 1 case of gastroenteritis, reported after MVA-BN-Filo vaccination and considered to be unrelated to study vaccine by the investigator, all grade 3 events were associated with a clinical laboratory abnormality. No remarkable trends were observed.
- Related events were observed in 7.4% (8/108) of Ad26.ZEBOV doses, 9.3% (10/108) of MVA-BN-Filo doses, and 6.4% (3/47) of placebo doses. The majority of related events were associated with a clinical laboratory abnormality. No remarkable trends were observed.

***Deaths, Serious Adverse Events, and Other Significant Adverse Events***

*HIV-uninfected Adult and Elderly Participants (Cohort 1)*

In total, 25 serious adverse events were reported in 22 participants (21 active vaccine recipients and 1 placebo recipient), including 1 event with an onset at screening (hepatitis C, not counted in the safety tables). Except for cellulitis (post Ad26.ZEBOV vaccination), cataract (post MVA-BN-Filo vaccination), and Meniere’s disease (post placebo), each reported in 1 participant, all serious adverse events reported

post vaccination occurred outside of the 28-day window for the analysis of unsolicited adverse events and therefore are not included in the tables below. None of the serious events in Cohort 1 were considered to be related to study vaccine by the investigator.

There were no deaths, IREs or adverse events leading to discontinuation of study vaccination.

*HIV-infected Adult Participants (Cohort 2a)*

Two active vaccine recipients in Cohort 2a each experienced one serious adverse event. Both events were reported outside of the 28-day window for the analysis of unsolicited adverse events and therefore are not counted in the tables below. One of the serious events was fatal (alcohol poisoning). Neither event was considered to be related to study vaccine by the investigator.

There were no IREs and no adverse events leading to discontinuation of study vaccination.

*Adolescents (Aged 12-17 Years) and Children (Aged 4-11 Years) (Cohorts 2b and 3)*

One participant in Cohort 2b experienced 2 serious adverse events, and 2 participants in Cohort 3 each experienced 1 serious adverse event. All serious events were reported outside of the 28-day window for analysis of unsolicited adverse events and therefore are not included in the tables below. The 2 events in the participant in Cohort 2b were fatal (typhoid fever and malaria). One of the serious events in Cohort 3 led to withdrawal from study vaccination (second-degree burns following a domestic accident). None of the serious events in Cohorts 2b and 3 were considered to be related to study vaccine by the investigator.

There were no IREs and no other adverse events leading to discontinuation of study vaccination.



**Table 11: Unsolicited Adverse Events: Summary – Healthy Adults and Elderly; Full Analysis Set**

	Cohort 1 (Healthy Adults and Elderly)					
	28-Day Interval		56-Day Interval		84-Day Interval	
	Ad26, MVA(, Ad26)	Placebo, Placebo(, Placebo)	Ad26, MVA(, Ad26)	Placebo, Placebo(, Placebo)	Ad26, MVA	Placebo, Placebo
Subjects with at least one	225	43	224	44	110	22
<b>Post-dose 1</b>						
unsolicited AE	96 (42.7%)	17 (39.5%)	68 (30.4%)	17 (38.6%)	37 (33.6%)	6 (27.3%)
unsolicited AE with severity grade 1 as worst grade	49 (21.8%)	11 (25.6%)	37 (16.5%)	7 (15.9%)	24 (21.8%)	3 (13.6%)
unsolicited AE with severity grade 2 as worst grade	31 (13.8%)	1 (2.3%)	24 (10.7%)	6 (13.6%)	10 (9.1%)	1 (4.5%)
unsolicited AE with severity grade 3 as worst grade	16 (7.1%)	5 (11.6%)	7 (3.1%)	4 (9.1%)	3 (2.7%)	2 (9.1%)
unsolicited AE that is related to vaccine	21 (9.3%)	4 (9.3%)	13 (5.8%)	5 (11.4%)	8 (7.3%)	1 (4.5%)
AE leading to permanent stop of vaccine	0	0	0	0	0	0
immediate reportable event	0	0	0	0	0	0
SAE	1 (0.4%)	0	0	0	0	0
SAE that is thought to be related to vaccine	0	0	0	0	0	0
AEs with fatal outcome	0	0	0	0	0	0
<b>Post-dose 2</b>	219	39	200	39	98	21
unsolicited AE	74 (33.8%)	15 (38.5%)	58 (29.0%)	13 (33.3%)	34 (34.7%)	7 (33.3%)
unsolicited AE with severity grade 1 as worst grade	42 (19.2%)	8 (20.5%)	29 (14.5%)	5 (12.8%)	21 (21.4%)	4 (19.0%)
unsolicited AE with severity grade 2 as worst grade	27 (12.3%)	6 (15.4%)	22 (11.0%)	6 (15.4%)	10 (10.2%)	2 (9.5%)
unsolicited AE with severity grade 3 as worst grade	5 (2.3%)	1 (2.6%)	7 (3.5%)	2 (5.1%)	3 (3.1%)	1 (4.8%)
unsolicited AE that is related to vaccine	10 (4.6%)	1 (2.6%)	15 (7.5%)	2 (5.1%)	5 (5.1%)	0
AE leading to permanent stop of vaccine	0	0	0	0	0	0
immediate reportable event	0	0	0	0	0	0
SAE	0	1 (2.6%)	1 (0.5%)	0	0	0
SAE that is thought to be related to vaccine	0	0	0	0	0	0
AEs with fatal outcome	0	0	0	0	0	0
<b>Post-dose 1 and Post-dose 2 Combined</b>	225	43	224	44	110	22
unsolicited AE	126 (56.0%)	24 (55.8%)	100 (44.6%)	25 (56.8%)	56 (50.9%)	13 (59.1%)
unsolicited AE with severity grade 1 as worst grade	60 (26.7%)	11 (25.6%)	44 (19.6%)	11 (25.0%)	32 (29.1%)	7 (31.8%)
unsolicited AE with severity grade 2 as worst grade	45 (20.0%)	7 (16.3%)	43 (19.2%)	9 (20.5%)	18 (16.4%)	3 (13.6%)
unsolicited AE with severity grade 3 as worst grade	21 (9.3%)	6 (14.0%)	13 (5.8%)	5 (11.4%)	6 (5.5%)	3 (13.6%)
unsolicited AE that is related to vaccine	28 (12.4%)	4 (9.3%)	27 (12.1%)	6 (13.6%)	13 (11.8%)	1 (4.5%)
AE leading to permanent stop of vaccine	0	0	0	0	0	0
immediate reportable event	0	0	0	0	0	0
SAE	1 (0.4%)	1 (2.3%)	1 (0.4%)	0	0	0
SAE that is thought to be related to vaccine	0	0	0	0	0	0
AEs with fatal outcome	0	0	0	0	0	0

**Table 11: Unsolicited Adverse Events: Summary – Healthy Adults and Elderly; Full Analysis Set**

	Cohort 1 (Healthy Adults and Elderly)					
	28-Day Interval		56-Day Interval		84-Day Interval	
	Ad26, MVA(, Ad26)	Placebo, Placebo(, Placebo)	Ad26, MVA(, Ad26)	Placebo, Placebo(, Placebo)	Ad26, MVA	Placebo, Placebo
Subjects with at least one	34	8	39	9	-	-
<b>Post-dose 3</b>						
unsolicited AE	9 (26.5%)	3 (37.5%)	14 (35.9%)	0		
unsolicited AE with severity grade 1 as worst grade	5 (14.7%)	2 (25.0%)	8 (20.5%)	0		
unsolicited AE with severity grade 2 as worst grade	4 (11.8%)	1 (12.5%)	3 (7.7%)	0		
unsolicited AE with severity grade 3 as worst grade	0	0	3 (7.7%)	0		
unsolicited AE that is related to vaccine	0	0	3 (7.7%)	0		
AE leading to permanent stop of vaccine	0	0	0	0		
immediate reportable event	0	0	0	0		
SAE	0	0	0	0		
SAE that is thought to be related to vaccine	0	0	0	0		
AEs with fatal outcome	0	0	0	0		

AE: adverse event; SAE: serious adverse event.

Note that vaccine relates to MVA-BN-Filo, Ad26.ZEBOV or placebo.

This table only includes adverse events that were reported between the dose 1 vaccination and 28 days post-dose 1, between dose 2 vaccination and 28 days post-dose 2, and between dose 3 vaccination and 28 days post-dose 3.

Immediate reportable event: any event of neuroimmunologic significance as defined in the protocol.

Ad26: Ad26.ZEBOV at a dose of  $5 \times 10^{10}$  vp; MVA: MVA-BN-Filo at a dose of  $1 \times 10^8$  Inf.U.

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**Table 12: Unsolicited Adverse Events: Summary – HIV-infected Adults; Full Analysis Set**

	Cohort 2a (HIV-infected)			
	28-Day Interval		56-Day Interval	
	Ad26, MVA	Placebo, Placebo	Ad26, MVA	Placebo, Placebo
Subjects with at least one				
<b>Post-dose 1</b>	59	12	59	12
unsolicited AE	25 (42.4%)	7 (58.3%)	25 (42.4%)	3 (25.0%)
unsolicited AE with severity grade 1 as worst grade	16 (27.1%)	5 (41.7%)	12 (20.3%)	0
unsolicited AE with severity grade 2 as worst grade	4 (6.8%)	0	9 (15.3%)	2 (16.7%)
unsolicited AE with severity grade 3 as worst grade	5 (8.5%)	2 (16.7%)	4 (6.8%)	1 (8.3%)
unsolicited AE that is related to vaccine	2 (3.4%)	2 (16.7%)	5 (8.5%)	0
AE leading to permanent stop of vaccine	0	0	0	0
immediate reportable event	0	0	0	0
SAE	0	0	0	0
SAE that is thought to be related to vaccine	0	0	0	0
AEs with fatal outcome	0	0	0	0
<b>Post-dose 2</b>	58	12	59	12
unsolicited AE	22 (37.9%)	4 (33.3%)	22 (37.3%)	4 (33.3%)
unsolicited AE with severity grade 1 as worst grade	14 (24.1%)	0	10 (16.9%)	2 (16.7%)
unsolicited AE with severity grade 2 as worst grade	7 (12.1%)	4 (33.3%)	9 (15.3%)	1 (8.3%)
unsolicited AE with severity grade 3 as worst grade	1 (1.7%)	0	3 (5.1%)	1 (8.3%)
unsolicited AE that is related to vaccine	3 (5.2%)	0	9 (15.3%)	1 (8.3%)
AE leading to permanent stop of vaccine	0	0	0	0
immediate reportable event	0	0	0	0
SAE	0	0	0	0
SAE that is thought to be related to vaccine	0	0	0	0
AEs with fatal outcome	0	0	0	0
<b>Post-dose 1 and Post-dose 2 Combined</b>	59	12	59	12
unsolicited AE	35 (59.3%)	9 (75.0%)	33 (55.9%)	5 (41.7%)
unsolicited AE with severity grade 1 as worst grade	19 (32.2%)	3 (25.0%)	13 (22.0%)	1 (8.3%)
unsolicited AE with severity grade 2 as worst grade	10 (16.9%)	4 (33.3%)	13 (22.0%)	2 (16.7%)
unsolicited AE with severity grade 3 as worst grade	6 (10.2%)	2 (16.7%)	7 (11.9%)	2 (16.7%)
unsolicited AE that is related to vaccine	4 (6.8%)	2 (16.7%)	13 (22.0%)	1 (8.3%)
AE leading to permanent stop of vaccine	0	0	0	0
immediate reportable event	0	0	0	0
SAE	0	0	0	0
SAE that is thought to be related to vaccine	0	0	0	0
AEs with fatal outcome	0	0	0	0

AE: adverse event; SAE: serious adverse event.

Note that vaccine relates to MVA-BN-Filo, Ad26.ZEBOV or placebo.

This table only includes adverse events that were reported between the dose 1 vaccination and 28 days post-dose 1, and between dose 2 vaccination and 28 days post-dose 2.

Immediate reportable event: any event of neuroimmunologic significance as defined in the protocol.

Ad26: Ad26.ZEBOV at a dose of  $5 \times 10^{10}$  vp; MVA: MVA-BN-Filo at a dose of  $1 \times 10^8$  Inf.U.

**Table 13: Unsolicited Adverse Events: Summary – Healthy Adolescents and Children; Full Analysis Set**

	Cohort 2b (12-17 Years)				Cohort 3 (4-11 Years)			
	28-Day Interval		56-Day Interval		28-Day Interval		56-Day Interval	
	Ad26, MVA	Placebo, Placebo	Ad26, MVA	Placebo, Placebo	Ad26, MVA	Placebo, Placebo	Ad26, MVA	Placebo, Placebo
Subjects with at least one								
<b>Post-dose 1</b>	55	11	55	10	54	12	54	12
unsolicited AE	28 (50.9%)	4 (36.4%)	31 (56.4%)	5 (50.0%)	23 (42.6%)	4 (33.3%)	19 (35.2%)	4 (33.3%)
unsolicited AE with severity grade 1 as worst grade	19 (34.5%)	2 (18.2%)	16 (29.1%)	3 (30.0%)	16 (29.6%)	2 (16.7%)	14 (25.9%)	3 (25.0%)
unsolicited AE with severity grade 2 as worst grade	5 (9.1%)	2 (18.2%)	8 (14.5%)	0	7 (13.0%)	2 (16.7%)	4 (7.4%)	1 (8.3%)
unsolicited AE with severity grade 3 as worst grade	4 (7.3%)	0	7 (12.7%)	2 (20.0%)	0	0	1 (1.9%)	0
unsolicited AE that is related to vaccine	4 (7.3%)	1 (9.1%)	10 (18.2%)	0	4 (7.4%)	1 (8.3%)	4 (7.4%)	1 (8.3%)
AE leading to permanent stop of vaccine	0	0	0	0	0	0	0	0
immediate reportable event	0	0	0	0	0	0	0	0
SAE	0	0	0	0	0	0	0	0
SAE that is thought to be related to vaccine	0	0	0	0	0	0	0	0
AEs with fatal outcome	0	0	0	0	0	0	0	0
<b>Post-dose 2</b>	55	10	54	10	54	12	54	11
unsolicited AE	18 (32.7%)	4 (40.0%)	26 (48.1%)	4 (40.0%)	20 (37.0%)	7 (58.3%)	22 (40.7%)	8 (72.7%)
unsolicited AE with severity grade 1 as worst grade	9 (16.4%)	2 (20.0%)	9 (16.7%)	4 (40.0%)	11 (20.4%)	6 (50.0%)	15 (27.8%)	5 (45.5%)
unsolicited AE with severity grade 2 as worst grade	7 (12.7%)	2 (20.0%)	13 (24.1%)	0	9 (16.7%)	1 (8.3%)	5 (9.3%)	3 (27.3%)
unsolicited AE with severity grade 3 as worst grade	2 (3.6%)	0	4 (7.4%)	0	0	0	2 (3.7%)	0
unsolicited AE that is related to vaccine	7 (12.7%)	3 (30.0%)	10 (18.5%)	0	7 (13.0%)	0	3 (5.6%)	1 (9.1%)
AE leading to permanent stop of vaccine	0	0	0	0	0	0	0	0
immediate reportable event	0	0	0	0	0	0	0	0
SAE	0	0	0	0	0	0	0	0
SAE that is thought to be related to vaccine	0	0	0	0	0	0	0	0
AEs with fatal outcome	0	0	0	0	0	0	0	0
<b>Post-dose 1 and Post-dose 2 Combined</b>	55	11	55	10	54	12	54	12
unsolicited AE	35 (63.6%)	5 (45.5%)	42 (76.4%)	6 (60.0%)	34 (63.0%)	9 (75.0%)	30 (55.6%)	9 (75.0%)
unsolicited AE with severity grade 1 as worst grade	19 (34.5%)	2 (18.2%)	16 (29.1%)	4 (40.0%)	21 (38.9%)	6 (50.0%)	20 (37.0%)	5 (41.7%)
unsolicited AE with severity grade 2 as worst grade	10 (18.2%)	3 (27.3%)	16 (29.1%)	0	13 (24.1%)	3 (25.0%)	7 (13.0%)	4 (33.3%)
unsolicited AE with severity grade 3 as worst grade	6 (10.9%)	0	10 (18.2%)	2 (20.0%)	0	0	3 (5.6%)	0
unsolicited AE that is related to vaccine	11 (20.0%)	3 (27.3%)	15 (27.3%)	0	9 (16.7%)	1 (8.3%)	6 (11.1%)	2 (16.7%)
AE leading to permanent stop of vaccine	0	0	0	0	0	0	0	0
immediate reportable event	0	0	0	0	0	0	0	0
SAE	0	0	0	0	0	0	0	0
SAE that is thought to be related to vaccine	0	0	0	0	0	0	0	0
AEs with fatal outcome	0	0	0	0	0	0	0	0

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**Table 13: Unsolicited Adverse Events: Summary – Healthy Adolescents and Children; Full Analysis Set**

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AE: adverse event; SAE: serious adverse event.

Note that vaccine relates to MVA-BN-Filo, Ad26.ZEBOV or placebo.

This table only includes adverse events that were reported between the dose 1 vaccination and 28 days post-dose 1, and between dose 2 vaccination and 28 days post-dose 2.

Immediate reportable event: any event of neuroimmunologic significance as defined in the protocol.

Ad26: Ad26.ZEBOV at a dose of  $5 \times 10^{10}$  vp; MVA: MVA-BN-Filo at a dose of  $1 \times 10^8$  Inf.U.

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***Clinical Laboratory Abnormalities***

The following analysis of clinical laboratory abnormalities includes abnormalities reported up to 28 days following each vaccination.

No remarkable trends were observed in grade 3 laboratory abnormalities in any of the cohorts (1, 2a, 2b, 3). The most frequently observed grade 3 laboratory abnormalities are summarized below.

***HIV-uninfected Adult and Elderly Participants (Cohort 1) - per FDA Toxicity Grading Scale***

- Grade 3 hyponatremia, observed in 3.8% (24/630) of Ad26.ZEBOV doses, 0.2% (1/516) of MVA-BN-Filo doses, 3.2% (7/222) of placebo doses.
- Grade 3 decrease in neutrophils, observed in 3.0% (19/630) of Ad26.ZEBOV doses, 3.1% (16/516) of MVA-BN-Filo doses, 4.5% (10/222) of placebo doses.

***HIV-infected Adult Participants (Cohort 2a) - per FDA Toxicity Grading Scale***

- Grade 3 decrease in neutrophils, observed in 4.2% (5/118) of Ad26.ZEBOV doses, 6.0% (7/116) of MVA-BN-Filo doses, 10.4% (5/48) of placebo doses.

***Adolescents (Aged 12-17 Years) (Cohort 2b) - per FDA Toxicity Grading Scale***

- Grade 3 hypernatremia, observed in 4.6% (5/109) of Ad26.ZEBOV doses, 5.6% (6/108) of MVA-BN-Filo doses, 4.9% (2/41) of placebo doses.
- Grade 3 hyponatremia, observed in 5.5% (6/109) of Ad26.ZEBOV doses, 0.9% (1/108) of MVA-BN-Filo doses, 2.4% (1/41) of placebo doses.
- Grade 3 decrease in neutrophils, observed in 5.5% (6/110) of Ad26.ZEBOV doses, 1.9% (2/108) of MVA-BN-Filo doses, 2.4% (1/41) of placebo doses.

***Children (Aged 4-11 Years) (Cohort 3) - per DMID Toxicity Grading Scale***

- All grade 3 laboratory abnormalities in Cohort 3 were observed only once with any study vaccine (Ad26.ZEBOV, MVA-BN-Filo, placebo), except for grade 3 hyponatremia which was reported on 2 occasions following Ad26.ZEBOV dosing (1.9% [2/108] of doses).

***Other Safety Observations***

No remarkable findings were observed for vital signs and physical examinations. One adolescent required a follow-up ECG after the dose 1 vaccination (placebo); the results were normal.

**IMMUNOGENICITY RESULTS:**

A summary of the vaccine-induced immune responses observed in the participants who received an Ad26, MVA regimen is provided below. Responses in placebo recipients were either low or not quantifiable and are not described here. In addition, the results of the analysis of Ad26 neutralizing antibody concentrations are briefly described for active vaccine as well as placebo recipients.

***Binding Antibody Responses Against EBOV GP (ELISA)******HIV-uninfected Adult and Elderly Participants (Cohort 1) (Table 14, Per Protocol Analysis Set)******Observations at Baseline***

Baseline sample interpretation was positive for EBOV GP-specific binding antibodies (ie, sample value above the LLOQ) in 105 participants who received an Ad26, MVA regimen: 55/169 (33%) participants in the 28-day interval group, 46/134 (34%) participants in the 56-day interval group, 4/26 (15%) participants in the 84-day interval group (data not tabulated in this Synopsis). The geometric mean concentrations (GMCs) at baseline were low (39 ELISA units/mL in the 56-day interval schedule) or below the LLOQ of 36.11 ELISA units/mL (in the 28-day and 84-day interval schedules).



*Binding Antibody Responses Observed at 21 Days Post Dose 2*

At 21 days post MVA-BN-Filo vaccination, binding antibody responses against EBOV GP were observed in 98% of participants in the 28-day interval schedule (GMC: 3085 ELISA units/mL), 99% of participants in the 56-day interval schedule (GMC: 7518 ELISA units/mL), and in 100% of participants in the 84-day interval schedule (GMC: 7300 ELISA units/mL).

The potential influence of a positive baseline EBOV GP FANG ELISA level was evaluated in post-hoc statistical analyses (ie, stratification of EBOV GP-specific binding antibody concentrations by baseline ELISA concentration, and a correlation analysis).

The EBOV GP-specific binding antibody responses were stratified by the following baseline EBOV GP ELISA levels: <LLOQ, LLOQ to 100, >100 to 1000, >1000 ELISA units/mL. Although some strata had a limited number of participants, overall, there was no apparent influence of the baseline EBOV GP ELISA level on vaccine-induced binding antibody responses.

A correlation analysis performed between baseline and 21 days post dose 2 binding antibody concentrations did not indicate an obvious positive (anamnestic response) or negative (immune interference) effect of the baseline ELISA values on the immunogenicity (Spearman correlation coefficients: 0.07 in the 28-day interval schedule, 0.08 in the 56-day interval schedule, and 0.13 in the 84-day interval schedule).

*Binding Antibody Responses Observed at Other Timepoints*

Prior to MVA-BN-Filo vaccination, binding antibody responses against EBOV GP were observed in 77% of participants in the 28-day interval schedule, 81% of participants in the 56-day interval schedule, and 81% of participants in the 56-day interval schedule. At this timepoint (Day 29, 57 or 85), the GMC values were similar across the 3 schedules (332 ELISA units/mL on Day 29, 361 ELISA units/mL on Day 57, 242 ELISA units/mL on Day 85).

Compared to 21 day post dose 2, the binding antibody concentrations were lower on Day 365 (1 year post dose 1) in all schedules, and responses were observed in 80% of the participants in the 28-day interval schedule (GMC: 313 ELISA units/mL), 78% of the participants in the 56-day interval schedule (GMC: 342 ELISA units/mL), and 89% of the participants in the 84-day interval schedules (GMC: 363 ELISA units/mL).

*Binding Antibody Responses Observed Post Booster Dose*

A booster dose of Ad26.ZEBOV was given at 1 year post dose 1 to a subset of 73 participants in the 28- and 56-day interval schedules of Cohort 1. On Day 372 (ie, 7 days post booster on Day 365), a ~55-fold increase in binding antibody concentrations was observed in both schedules when compared to the pre-booster timepoint on Day 365 (GMCs: 16639 ELISA units/mL versus 301 ELISA units/mL in the 28-day interval schedule; and 20416 ELISA units/mL versus 366 ELISA units/mL in the 56-day interval schedule) (responder rate: 100%).

In both schedules (28- and 56-day interval), the binding antibody concentrations further increased towards the 21-day post-booster dose timepoint (Day 386) (GMCs: 29315 ELISA units/mL in the 28-day interval schedule and 41643 ELISA units/mL in the 56-day interval schedule) (responder rate: 100%). Of note, the GMCs at the 21-day post-booster dose timepoint were about 5- to 10-fold higher compared to those at 21 days post dose 2.

Compared to the 21-day post-booster dose timepoint (Day 386), the binding antibody concentrations were lower on Day 729 (1 year post booster dose); yet, responses were observed in 97% to 100% of participants at a level approximately 10-fold higher than at 1 year post dose 1 (GMCs: 4534 ELISA units/mL versus 313 ELISA units/mL in the 28-day interval schedule; 4383 ELISA units/mL versus 342 ELISA units/mL in the 56-day interval schedule).

*Impact of a Delay in Dose 2 or in the Booster Dose*

A sensitivity analysis was performed on the Immunogenicity Analysis Set to show data for participants who received dose 2 at 28, 56 or 84 days post dose 1 (N=348, active; N=64, placebo) versus those who received dose 2 later (up to 483 days post dose 1) mainly because of the study pause (N=169, active; N=35, placebo). The results showed that extension of the interval between dose 1 and dose 2 beyond 84 days (up to 483 days) did not negatively impact the vaccine-induced immune responses. At 21 days post dose 2, binding antibody responses against EBOV GP were observed in 98% to 100% of the participants who received an Ad26, MVA regimen, with a trend for higher numerical GMC values with increasing intervals between dose 1 and dose 2.

The analysis on the Immunogenicity Analysis Set was also repeated to show data for the participants who received the booster dose in the Cohort 1 substudy within 30 days of Day 365 post dose 1 (N=39, active; N=8, placebo) versus those who received the booster dose beyond 30 days of Day 365 post dose 1 (N=34, active; N=9, placebo). At the 21-day post-booster timepoint, binding antibody responses against EBOV GP were observed in all (100%) participants, regardless of the timing of the booster dose, with GMCs being generally similar across groups.

***Binding Antibody Responses Against EBOV GP (ELISA)******HIV-infected Adult Participants (Cohort 2a) (Table 15, Per Protocol Analysis Set)****Observations at Baseline*

Baseline sample interpretation was positive for EBOV GP-specific binding antibodies (ie, sample value above the LLOQ) in 27 participants who received an Ad26, MVA regimen: 13/58 (22%) participants in the 28-day interval schedule, 14/58 (24%) participants in the 56-day interval schedule (data not tabulated in this Synopsis). The GMCs at baseline were below the LLOQ of 36.11 ELISA units/mL.

*Binding Antibody Responses Observed at 21 Days Post Dose 2*

At 21 days post MVA-BN-Filo vaccination, binding antibody responses against EBOV GP were observed in 100% of participants in the 28-day and 56-day interval schedules, with similar GMC values between schedules (4207 ELISA units/mL and 5283 ELISA units/mL).

*Binding Antibody Responses Observed at Other Timepoints*

Prior to MVA-BN-Filo vaccination, binding antibody responses against EBOV GP were observed in 81% of participants in the 28-day interval schedule and in 88% of participants in the 56-day interval schedule. At this timepoint (Day 29 or 57), the GMCs were similar across the schedules (368 ELISA units/mL on Day 29 and 291 ELISA units/mL on Day 57).

Compared to 21 days post dose 2, binding antibody concentrations were lower on Day 365 (1 year post dose 1) in both schedules; yet, responses were observed in 86% of participants in the 28-day interval schedule (GMC: 459 ELISA units/mL) and 88% of participants in the 56-day interval schedule (GMC: 338 ELISA units/mL).

*Binding Antibody Responses by Baseline Sample Positivity*

Similar to Cohort 1, post-hoc analyses of the immunogenicity by baseline EBOV GP ELISA level were performed to investigate any potential influence of EBOV GP-binding antibodies present at baseline on vaccine-induced responses (ie, stratification of EBOV GP-specific binding antibody concentrations at all timepoints by baseline ELISA concentration, and a correlation analysis at 21 days post dose 2). Although some strata had a limited number of participants, overall, there was no apparent influence of the baseline EBOV GP ELISA level on vaccine-induced binding antibody responses. Also, a negligible correlation was observed between the ELISA values at 21 days post dose 2 and those at baseline on an individual level (Spearman correlation coefficients: 0.12 in the 28-day interval schedule and -0.09 in the 56-day interval schedule).

***Binding Antibody Responses Against EBOV GP (ELISA)******Adolescents (Aged 12-17 years) (Cohort 2b) (Table 16, Per Protocol Analysis Set)******Observations at Baseline***

Baseline sample interpretation was positive for EBOV GP-specific binding antibodies (ie, sample value above the LLOQ) in 33 adolescents who received an Ad26,MVA regimen: 15/54 (28%) in the 28-day interval schedule and 18/53 (34%) in the 56-day interval schedule (data not tabulated in this Synopsis). The baseline GMCs were below the LLOQ of 36.11 ELISA units/mL.

***Binding Antibody Responses Observed at 21 Days Post Dose 2***

At 21 days post MVA-BN-Filo vaccination, binding antibody responses against EBOV GP were observed in 100% of participants in both the 28-day interval schedule (GMC: 6993 ELISA units/mL) and 56-day interval schedule (GMC: 13532 ELISA units/mL).

***Binding Antibody Responses Observed at Other Timepoints***

Prior to MVA-BN-Filo vaccination, binding antibody responses against EBOV GP were observed in 93% of participants in the 28-day interval schedule and in 94% of participants in the 56-day interval schedule. At this timepoint (Day 29 or 57), the GMCs were similar across the schedules (619 ELISA units/mL on Day 29 and 562 ELISA units/mL on Day 57).

Compared to 21 days post dose 2, binding antibody concentrations were lower on Day 365 (1 year post dose 1) in both schedules; responses were observed in 92% of participants in the 28-day interval schedule (GMC: 593 ELISA units/mL) and 90% of participants in the 56-day interval schedule (GMC: 541 ELISA units/mL).

***Binding Antibody Responses by Baseline Sample Positivity***

Similar to Cohort 1, post-hoc analyses of the immunogenicity by baseline EBOV GP ELISA level were performed to evaluate any potential influence of EBOV GP-binding antibodies present at baseline on vaccine-induced responses (ie, stratification of EBOV GP-specific binding antibody concentrations at all timepoints by baseline ELISA concentration, and a correlation analysis at 21 days post dose 2). Although some strata had a limited number of participants, overall, there was no apparent influence of the baseline EBOV GP ELISA level on vaccine-induced binding antibody responses. Also, a negligible correlation was observed between the ELISA values at 21 days post dose 2 and those at baseline on an individual level (Spearman correlation coefficients: 0.05 in the 28-day interval schedule and -0.14 in the 56-day interval schedule).

***Binding Antibody Responses Against EBOV GP (ELISA)******Children (Aged 4-11 years) (Cohort 3) (Table 16, Per Protocol Analysis Set)******Observations at Baseline***

Baseline sample interpretation was positive for EBOV GP-specific binding antibodies (ie, sample value above the LLOQ) in 18 participants who received an Ad26,MVA regimen: 10/53 (19%) in the 28-day interval schedule and 8/52 (15%) in the 56-day interval schedule (data not tabulated in this Synopsis). The baseline GMCs were below the LLOQ of 36.11 ELISA units/mL.

***Binding Antibody Responses Observed at 21 Days Post Dose 2***

At 21 days post MVA-BN-Filo vaccination, binding antibody responses against EBOV GP were observed in 100% of participants in both the 28-day interval schedule (GMC: 8007 ELISA units/mL) and 56-day interval schedule (GMC: 17388 ELISA units/mL).

*Binding Antibody Responses Observed at Other Timepoints*

Prior to MVA-BN-Filo vaccination, binding antibody responses against EBOV GP were observed in 96% of participants in the 28-day interval schedule and in 98% of participants in the 56-day interval schedule. At this timepoint (Day 29 or 57), the GMCs were similar across schedules (713 ELISA units/mL on Day 29 and 658 ELISA units/mL on Day 57).

Compared to 21 days post dose 2, the binding antibody concentrations were lower on Day 365 (1 year post dose 1) in both schedules; responses were observed in 96% of the participants in the 28-day interval schedule (GMC: 981 ELISA units/mL) and 98% of the participants in the 56-day interval schedule (GMC: 637 ELISA units/mL).

*Binding Antibody Responses by Baseline Sample Positivity*

Similar to Cohort 1, post-hoc analyses of the immunogenicity by baseline EBOV GP ELISA level were performed to evaluate any potential influence of EBOV GP-binding antibodies present at baseline on vaccine-induced responses (ie, stratification of EBOV GP-specific binding antibody concentrations at all timepoints by baseline ELISA concentration, and a correlation analysis at 21 days post dose 2). Although some strata had a limited number of participants, overall, there was no apparent influence of the baseline EBOV GP ELISA level on vaccine-induced binding antibody responses. Also, a negligible correlation was observed between ELISA values at 21 days post dose 2 and those at baseline on an individual level (Spearman correlation coefficients: 0.09 in the 28-day interval schedule and 0.14 in the 56-day interval schedule).

**Table 14: EBOV GP-Specific Binding Antibody Responses (ELISA, ELISA units/mL): Geometric Means and Responder Rates – Healthy Adults and Elderly; Per Protocol Analysis Set**

	Cohort 1 (Healthy Adults and Elderly)		
	28-Day Interval	56-Day Interval	84-Day Interval
	Ad26, MVA(, Ad26)	Ad26, MVA(, Ad26)	Ad26, MVA
Day 1 (Baseline)			
N	169	134	26
GMC (95% CI)	<LLOQ (<LLOQ; 41)	39 (<LLOQ; 48)	<LLOQ (<LLOQ; 41)
Day 29 (28 days post-dose 1)			
N	173	-	-
GMC (95% CI)	332 (282; 390)		
Responder (n/N* (%))	130/169 (76.9%)		
Day 50 (21 days post-dose 2)			
N	171	-	-
GMC (95% CI)	3085 (2648; 3594)		
Responder (n/N* (%))	164/167 (98.2%)		
Day 57 (56 days post-dose 1)			
N	-	136	-
GMC (95% CI)		361 (307; 423)	
Responder (n/N* (%))		107/133 (80.5%)	
Day 78 (21 days post-dose 2)			
N	-	136	-
GMC (95% CI)		7518 (6468; 8740)	
Responder (n/N* (%))		132/133 (99.2%)	
Day 85 (84 days post-dose 1)			
N	-	-	27
GMC (95% CI)			242 (181; 323)
Responder (n/N* (%))			21/26 (80.8%)

**Table 14: EBOV GP-Specific Binding Antibody Responses (ELISA, ELISA units/mL): Geometric Means and Responder Rates – Healthy Adults and Elderly; Per Protocol Analysis Set**

	Cohort 1 (Healthy Adults and Elderly)		
	28-Day Interval	56-Day Interval	84-Day Interval
	Ad26, MVA(, Ad26)	Ad26, MVA(, Ad26)	Ad26, MVA
Day 106 (21 days post-dose 2)			
N	-	-	27
GMC (95% CI)			7300 (5116; 10417)
Responder (n/N* (%))			26/26 (100.0%)
Day 365 (364 days post-dose 1)			
N	167	133	27
GMC (95% CI)	313 (271; 361)	342 (291; 401)	363 (234; 562)
Responder (n/N* (%))	130/163 (79.8%)	101/130 (77.7%)	23/26 (88.5%)
Day 365 (Pre-dose 3)			
N	32	39	-
GMC (95% CI)	301 (215; 422)	366 (273; 491)	
Responder (n/N* (%))	23/30 (76.7%)	26/37 (70.3%)	
Day 369 (4 days post-dose 3)			
N	33	39	-
GMC (95% CI)	386 (268; 558)	551 (401; 756)	
Responder (n/N* (%))	24/31 (77.4%)	27/37 (73.0%)	
Day 372 (7 days post-dose 3)			
N	33	39	-
GMC (95% CI)	16639 (12567; 22030)	20416 (15432; 27009)	
Responder (n/N* (%))	31/31 (100.0%)	37/37 (100.0%)	
Day 386 (21 days post-dose 3)			
N	33	39	-
GMC (95% CI)	29315 (20614; 41689)	41643 (32045; 54116)	
Responder (n/N* (%))	31/31 (100.0%)	37/37 (100.0%)	
Day 729 (364 days post-dose 3)			
N	32	37	-
GMC (95% CI)	4534 (2911; 7060)	4383 (2969; 6470)	
Responder (n/N* (%))	30/30 (100.0%)	34/35 (97.1%)	

N: number of subjects with data at that timepoint; N\*: number of subjects with data at baseline and at that timepoint

CI: confidence interval; GMC: geometric mean concentration; LLOQ: lower limit of quantification

A subject was a responder at a considered timepoint if the sample interpretation was negative at baseline and positive post baseline and the post-baseline value was greater than 2.5x LLOQ, or sample interpretation was positive both at baseline and post baseline and there was a greater than 2.5-fold increase from baseline.

Geometric mean concentration and corresponding confidence interval (CI) are shown on the reported scale (ELISA units/mL).

Ad26: Ad26.ZEBOV at a dose of  $5 \times 10^{10}$  vp; MVA: MVA-BN-Filo at a dose of  $1 \times 10^8$  Inf.U.

**Table 15: EBOV GP-Specific Binding Antibody Responses (ELISA, ELISA units/mL): Geometric Means and Responder Rates – HIV-infected Adults; Per Protocol Analysis Set**

	Cohort 2a (HIV-infected)	
	28-Day Interval	56-Day Interval
	Ad26, MVA	Ad26, MVA
Day 1 (Baseline)		
N	58	58
GMC (95% CI)	<LLOQ (<LLOQ; 38)	<LLOQ (<LLOQ; <LLOQ)
Day 29 (28 days post-dose 1)		
N	58	-
GMC (95% CI)	368 (272; 497)	
Responder (n/N* (%))	47/58 (81.0%)	
Day 50 (21 days post-dose 2)		
N	58	-
GMC (95% CI)	4207 (3233; 5474)	
Responder (n/N* (%))	58/58 (100.0%)	
Day 57 (56 days post-dose 1)		
N	-	59
GMC (95% CI)		291 (233; 364)
Responder (n/N* (%))		51/58 (87.9%)
Day 78 (21 days post-dose 2)		
N	-	59
GMC (95% CI)		5283 (4094; 6817)
Responder (n/N* (%))		58/58 (100.0%)
Day 365 (364 days post-dose 1)		
N	56	59
GMC (95% CI)	459 (352; 600)	338 (253; 450)
Responder (n/N* (%))	48/56 (85.7%)	51/58 (87.9%)

N: number of subjects with data at that timepoint; N\*: number of subjects with data at baseline and at that timepoint

CI: confidence interval; GMC: geometric mean concentration; LLOQ: lower limit of quantification

A subject was a responder at a considered timepoint if the sample interpretation was negative at baseline and positive post baseline and the post-baseline value was greater than 2.5x LLOQ, or sample interpretation was positive both at baseline and post baseline and there was a greater than 2.5-fold increase from baseline.

Geometric mean concentration and corresponding confidence interval (CI) are shown on the reported scale (ELISA units/mL).

Ad26: Ad26.ZEBOV at a dose of  $5 \times 10^{10}$  vp; MVA: MVA-BN-Filo at a dose of  $1 \times 10^8$  Inf.U.

**Table 16: EBOV GP-Specific Binding Antibody Responses (ELISA, ELISA units/mL): Geometric Means and Responder Rates – Healthy Adolescents and Children; Per Protocol Analysis Set**

	Cohort 2b (12-17 Years)		Cohort 3 (4-11 Years)	
	28-Day Interval	56-Day Interval	28-Day Interval	56-Day Interval
	Ad26, MVA	Ad26, MVA	Ad26, MVA	Ad26, MVA
Day 1 (Baseline)				
N	54	53	53	52
GMC (95% CI)	<LLOQ (<LLOQ; 45)	<LLOQ (<LLOQ; 37)	<LLOQ (<LLOQ; <LLOQ)	<LLOQ (<LLOQ; <LLOQ)
Day 29 (28 days post-dose 1)				
N	54	-	53	-
GMC (95% CI)	619 (490; 782)		713 (589; 861)	
Responder (n/N* (%))	50/54 (92.6%)		51/53 (96.2%)	
Day 50 (21 days post-dose 2)				
N	53	-	53	-
GMC (95% CI)	6993 (5256; 9303)		8007 (6321; 10142)	
Responder (n/N* (%))	53/53 (100.0%)		53/53 (100.0%)	



**Table 16: EBOV GP-Specific Binding Antibody Responses (ELISA, ELISA units/mL): Geometric Means and Responder Rates – Healthy Adolescents and Children; Per Protocol Analysis Set**

	Cohort 2b (12-17 Years)		Cohort 3 (4-11 Years)	
	28-Day Interval	56-Day Interval	28-Day Interval	56-Day Interval
	Ad26, MVA	Ad26, MVA	Ad26, MVA	Ad26, MVA
Day 57 (56 days post-dose 1)				
N	-	53	-	54
GMC (95% CI)		562 (460; 686)		658 (556; 780)
Responder (n/N* (%))		50/53 (94.3%)		51/52 (98.1%)
Day 78 (21 days post-dose 2)				
N	-	53	-	53
GMC (95% CI)		13532 (10732; 17061)		17388 (12973; 23306)
Responder (n/N* (%))		53/53 (100.0%)		51/51 (100.0%)
Day 209 (180 days post-dose 2)				
N	41	-	52	-
GMC (95% CI)	565 (463; 689)		841 (721; 980)	
Responder (n/N* (%))	38/41 (92.7%)		51/52 (98.1%)	
Day 237 (180 days post-dose 2)				
N	-	41	-	53
GMC (95% CI)		577 (454; 734)		715 (602; 851)
Responder (n/N* (%))		38/41 (92.7%)		51/52 (98.1%)
Day 365 (364 days post-dose 1)				
N	50	52	53	54
GMC (95% CI)	593 (477; 738)	541 (433; 678)	981 (814; 1183)	637 (529; 767)
Responder (n/N* (%))	46/50 (92.0%)	47/52 (90.4%)	51/53 (96.2%)	51/52 (98.1%)

N: number of subjects with data at that timepoint; N\*: number of subjects with data at baseline and at that timepoint

CI: confidence interval; GMC: geometric mean concentration; LLOQ: lower limit of quantification

A subject was a responder at a considered timepoint if the sample interpretation was negative at baseline and positive post baseline and the post-baseline value was greater than 2.5x LLOQ, or sample interpretation was positive both at baseline and post baseline and there was a greater than 2.5-fold increase from baseline.

Geometric mean concentration and corresponding confidence interval (CI) are shown on the reported scale (ELISA units/mL).

Ad26: Ad26.ZEBOV at a dose of  $5 \times 10^{10}$  vp; MVA: MVA-BN-Filo at a dose of  $1 \times 10^8$  Inf.U.

### ***Neutralizing Antibody Responses Against EBOV GP (psVNA)***

#### ***HIV-uninfected Adult and Elderly Participants (Cohort 1) (Per Protocol Analysis Set)***

Neutralizing antibody concentrations were determined at baseline, 21 days post dose 2, and 1 year post dose 1 in a subset (19%) of the participants in Cohort 1 who were assigned to the 28-day (N=50/268; 41 active and 9 placebo) and 56-day (N=50/268; 38 active and 12 placebo) interval schedules.

At 21 days post MVA-BN-Filo vaccination, neutralizing antibody responses to EBOV GP were observed in 92% of participants in the 28-day interval schedule (geometric mean titer [GMT]: 982 IC<sub>50</sub> titer [95% CI: 714; 1350]) and in 97% of participants in the 56-day interval schedule (GMT: 4100 IC<sub>50</sub> titer [95% CI: 2927; 5745]).

Compared to 21 days post dose 2, neutralizing antibody titers were lower on Day 365 (1 year post dose 1); responses were observed in 21% of the participants in the 28-day interval schedule (GMT: 123 IC<sub>50</sub> titer [95% CI: <LLOQ; 165]) and 24% of the participants in the 56-day interval schedule (GMT: 153 IC<sub>50</sub> titer [95% CI: <LLOQ; 210]).

A strong positive correlation was observed between binding antibody concentrations and the neutralizing antibody titers and (Spearman correlation coefficients: 0.799 at 21 days post dose 2 and 0.708 at 1 year post dose 1).

***IFN- $\gamma$  Producing T-cell Responses Against EBOV GP (IFN- $\gamma$  ELISpot)******HIV-uninfected Adult and Elderly Participants (Cohort 1) (Per Protocol Analysis Set)***

The IFN- $\gamma$  producing T-cell response was determined at baseline, 21 days post dose 2, and 1 year post dose 1 in a subset (31%) of the participants in Cohort 1 assigned to the 28 day (N=46/268; 37 active and 9 placebo) and 56-day (N=38/268; 31 active and 7 placebo) interval schedules.

At 21 days post MVA-BN-Filo vaccination, EBOV GP-specific IFN- $\gamma$  producing T-cell responses were observed in 27% of the participants in both schedules. The median IFN- $\gamma$  producing T-cell response, expressed as spot-forming units per million peripheral blood mononuclear cells (SFU/ $10^6$  PBMC), was 73 SFU/ $10^6$  PBMC (IQR: <50; 148) in the 28-day interval schedule and 61 SFU/ $10^6$  PBMC (IQR: <50; 105) in the 56-day interval schedule. At 1 year post dose 1 (Day 365), responses were observed in 18% of participants in the 28-day interval schedule and 7% of participants in the 56-day interval schedule. The median values at 1 year post dose 1 were <50 SFU/ $10^6$  PBMC.

***IFN- $\gamma$  Producing T-cell Responses Against EBOV GP (IFN- $\gamma$  ELISpot)******HIV-infected Adult Participants (Cohort 2a) (Per Protocol Analysis Set)***

The IFN- $\gamma$  producing T-cell response was determined at baseline, 21 days post dose 2, and 1 year post dose 1 in a subset (21%) of participants in Cohort 2a assigned to the 56-day interval schedule (N=15/71; 13 active and 2 placebo).

At 21 days post MVA-BN-Filo vaccination, EBOV GP-specific IFN- $\gamma$  producing T-cell responses were observed in 17% of participants. The median IFN- $\gamma$  producing T-cell response at this timepoint was below the positivity threshold of <50 SFU/ $10^6$  PBMC. At 1 year post dose 1 (Day 365), IFN- $\gamma$  producing T-cell responses were observed in 17% of the participants (median: <50 SFU/ $10^6$  PBMC), including one of the participants who responded at 21 days post dose 2.

***IFN- $\gamma$  Producing T-cell Responses Against EBOV GP (IFN- $\gamma$  ELISpot)******Adolescents (Aged 12-17 years) (Cohort 2b) (Per Protocol Analysis Set)***

The IFN- $\gamma$  producing T-cell response was determined at baseline, 21 days post dose 2, 6 months post dose 2, and 1 year post dose 1 in a subset (27%) of participants in Cohort 2b assigned to the 28-day (N=16/131; 14 active and 2 placebo) and 56-day (N=19/131; 15 active and 4 placebo) interval schedules.

At 21 days post MVA-BN-Filo vaccination, EBOV GP-specific IFN- $\gamma$  producing T-cell responses were observed in 13% of the participants in the 28-day interval schedule (median: 63 SFU/ $10^6$  PBMC [IQR: <50; 152]) and 29% of the participants in the 56-day interval schedule (median: 99 SFU/ $10^6$  PBMC [IQR: <50; 122]). At the 6-month post-dose 2 and 1-year post-dose 1 timepoints, the median IFN- $\gamma$  producing T-cell response was declined to a value <50 SFU/ $10^6$  PBMC in both vaccination schedules (28-day and 56-day interval); the responder rates were 0%.

***IFN- $\gamma$  Producing T-cell Responses Against EBOV GP (IFN- $\gamma$  ELISpot)******Children (Aged 4-11 years) (Cohort 3) (Per Protocol Analysis Set)***

The IFN- $\gamma$  producing T-cell response was determined at baseline, 21 days post dose 2, 6 months post dose 2, and 1 year post dose 1 in a subset (18%) of participants in Cohort 3 assigned to the 28 day (N=12/132; 11 active and 1 placebo) and 56-day (N=12/132; 10 active and 2 placebo) interval schedules.

At 21 days post MVA-BN-Filo vaccination, EBOV GP-specific IFN- $\gamma$  producing T-cell responses were observed in 50% of the participants in the 28-day interval schedule (median: 66 SFU/ $10^6$  PBMC [IQR: <50; 130]) and 25% of the participants in the 56-day interval schedule (median: 70 SFU/ $10^6$  PBMC [IQR: <50; 117]). At the 6-month post-dose 2 and 1-year post-dose 1 timepoints, the median IFN- $\gamma$  producing

T-cell response was declined to a value  $<50$  SFU/ $10^6$  PBMC in both vaccination schedules (28-day and 56-day interval); the responder rates were 0%.

### ***CD4+ and CD8+ T-cell Responses Against EBOV GP (ICS)***

#### ***HIV-uninfected Adult and Elderly Participants (Cohort 1) (Per Protocol Analysis Set)***

IFN- $\gamma$  and/or IL-2 and/or TNF- $\alpha$  producing CD4+ and CD8+ T-cells were determined at baseline, 21 days post dose 2, and 1 year post dose 1 in a subset (31%) of participants in Cohort 1 assigned to the 28-day (N=46/268; 37 active and 9 placebo) and 56-day (N=38/268; 31 active and 7 placebo) interval schedules.

CD4+ T-cell responses were observed in a substantial percentage of participants at 21 days post dose 2 for both the 28-day (50%) and 56-day interval (32%) schedule. The median percentage of CD4+ T-cells producing at least 1 of the 3 investigated cytokines (IFN- $\gamma$ , IL-2 and TNF- $\alpha$ ) tended to be higher for the 28-day interval schedule (0.11% [IQR: 0.04%; 0.16%]) compared to the 56-day interval schedule (0.06% [IQR:  $<$ LLOQ; 0.14%]). At 1 year post dose 1 (Day 365), CD4+ T-cell responses were observed in 7% of the participants in the 28-day interval schedule (median:  $<$ LLOQ) and 9% of the participants in the 56-day interval schedule (median:  $<$ LLOQ).

EBOV GP-specific CD8+ T-cell responses were observed at 21 days post dose 2 in 29% of the participants in the 28-day interval schedule (median: 0.05% [IQR:  $<$ LLOQ; 0.14%]) and 30% of the participants in the 56-day interval (median:  $<$ LLOQ). At 1 year post dose 1 (Day 365), CD8+ T-cell responses were observed in 16% of participants in the 28-day interval schedule (median:  $<$ LLOQ) versus 3% of participants in the 56-day interval schedule (median:  $<$ LLOQ).

### ***CD4+ and CD8+ T-cell Responses Against EBOV GP (ICS)***

#### ***HIV-infected Adult Participants (Cohort 2a) (Per Protocol Analysis Set)***

IFN- $\gamma$  and/or IL-2 and/or TNF- $\alpha$  producing CD4+ and CD8+ T-cells were determined at baseline, 21 days post dose 2, and 1 year post dose 1 in a subset (21%) of participants in Cohort 2a assigned to the 56-day interval schedule (N=15/71; 13 active and 2 placebo).

CD4+ T-cell responses were observed in 40% of the participants at 21 days post dose 2 (median: 0.18% [IQR:  $<$ LLOQ; 0.27%]) and in 27% of the participants at 1 year post dose 1 (Day 365) (median: 0.06% [IQR:  $<$ LLOQ; 0.12%]).

CD8+ T-cell responses were observed in 17% of the participants at 21 days post dose 2 (median:  $<$ LLOQ). At 1 year post dose 1 (Day 365), sample interpretation was positive in 1 participant, but this participant did not meet the responder criteria.

### ***CD4+ and CD8+ T-cell Responses Against EBOV GP (ICS)***

#### ***Adolescents (Aged 12-17 years) (Cohort 2b) (Per Protocol Analysis Set)***

IFN- $\gamma$  and/or IL-2 and/or TNF- $\alpha$  producing CD4+ and CD8+ T-cells were determined at baseline, 21 days post dose 2, 6 months post dose 2, and 1 year post dose 1 in a subset (29%) of participants in Cohort 2b assigned to the 28 day (N=18/131; 14 active and 4 placebo) and 56-day (N=20/131; 16 active and 4 placebo) interval schedules.

At 21 days post MVA-BN-Filo vaccination, CD4+ T-cell responses were observed in 40% of participants in both the 28-day interval schedule (median: 0.08% [IQR:  $<$ LLOQ; 0.17%]) and 56-day interval schedule (median: 0.08% [IQR:  $<$ LLOQ; 0.11%]). No CD8+ T-cell responses were observed at this timepoint. At the 6-month post-dose 2 and 1-year post-dose 1 timepoints, CD4+ and CD8+ T-cell responses were either low or not quantifiable.

***CD4+ and CD8+ T-cell Responses Against EBOV GP (ICS)******Children (Aged 4-11 years) (Cohort 3) (Per Protocol Analysis Set)***

IFN- $\gamma$  and/or IL-2 and/or TNF- $\alpha$  producing CD4+ and CD8+ T-cells were determined at baseline, 21 days post dose 2, 6 months post dose 2, and 1 year post dose 1 in a subset (22%) of participants in Cohort 3 assigned to the 28 day (N=15/132; 13 active and 2 placebo) and 56-day (N=14/132; 11 active and 3 placebo) interval schedules.

At 21 days post MVA-BN-Filo vaccination, CD4+ T-cell responses were observed in 60% of participants in the 28-day interval schedule and 33% of participants in the 56-day interval schedule. The median value at this timepoint tended to be higher for the 28-day interval schedule (0.19% [IQR: 0.10%; 0.30%]) than for the 56-day interval schedule (0.07% [IQR: <LLOQ; 0.23%]), and also higher than in the adolescents (0.08% in both the 28-day and 56-day interval schedule, see above). CD4+ T-cell responses were either low or not quantifiable at the 6-month post-dose 2 and 1-year post-dose 1 timepoints.

At 21 days post MVA-BN-Filo vaccination, CD8+ T-cell responses were observed in a small group of the participants (18%) in the 28-day interval schedule (median: <LLOQ). CD8+ T-cell responses were either low or not quantifiable at the 6-month post-dose 2 and 1-year post-dose 1 timepoints.

***Binding Antibody Responses Against MARV GP and SUDV GP (ELISA)******HIV-uninfected Adult and Elderly Participants (Cohort 1) (Per Protocol Analysis Set)***

MARV and SUDV GP-specific binding antibody concentrations were measured at baseline and 21 days post dose 2 in a subset (13%, 30/224) of the participants in Cohort 1 assigned to the Ad26, MVA 56-day interval schedule.

One (3.3%) participant had a low MARV GP-specific binding antibody concentration at baseline (prior to dose 1) (observed value: 23 ELISA units/mL). A similar level of MARV GP-specific binding antibodies was observed at 21 days post dose 2 in the same participant (observed value: 37 ELISA units/mL). No MARV GP-specific binding antibodies were detected in any of the other participants analyzed.

In total, 4 (13.3%) participants were positive for SUDV GP-specific binding antibodies at baseline (prior to dose 1) (observed values: 38, 50, 136 and 174 ELISA units/mL). At 21 days post dose 2, this number was increased to 29 (97%) participants (GMC: 142 ELISA units/mL; responder rate: 87%).

The participant with MARV GP-specific binding antibodies at 21 days post dose 2 also had EBOV and SUDV GP-specific binding antibodies at this timepoint. In addition, all 29 participants with SUDV GP-specific binding antibodies at 21 days post dose 2 also had EBOV GP-specific binding antibodies at this timepoint.

In order to evaluate how many participants with a SUDV GP- or MARV GP-specific binding antibody response also mounted an EBOV GP-specific binding antibody response, and to visualize the respective antibody concentrations, a correlation analysis was performed at 21 days post dose 2. At this timepoint, the correlation plot suggested a moderate positive correlation between EBOV GP- and SUDV GP-specific binding antibody concentrations (Spearman correlation coefficient: 0.656). Because only 1 participant had MARV GP-specific binding antibodies, no conclusion can be drawn on the potential correlations between MARV GP and EBOV GP, and between MARV GP and SUDV GP binding antibody responses.

***Immune Responses Against the Ad26 Vector Backbone (Ad26 VNA)******All Cohorts (1, 2a, 2b and 3) (Per Protocol Analysis Set)***

In Cohort 1, neutralizing antibodies against the Ad26 vector backbone were measured at baseline and at Day 365 (1 year post dose 1) in a subset (19%) of the participants assigned to the 28-day (N=76/268; 64 active and 12 placebo) and 56-day (N=81/268; 66 active and 15 placebo) interval schedules. In

Cohorts 2a, 2b and 3, neutralizing antibodies against the Ad26 vector backbone were measured at baseline in all participants (active and placebo).

In all cohorts (1, 2a, 2b, and 3), the majority of participants had Ad26 neutralizing antibodies at baseline (ie, prior to dosing on Day 1), indicating prior infection with Ad26 serotype:

- 82% of active vaccine recipients in the 28-day interval schedule (89% for placebo) and 97% of active vaccine recipients in the 56-day interval schedule (100% for placebo) in Cohort 1.
- 78% of active vaccine recipients in the 28-day interval schedule (91% for placebo) and 86% of active vaccine recipients in the 56-day interval schedule (92% for placebo) in Cohort 2a.
- 89% of active vaccine recipients (80% for placebo) in both the 28-day and 56-day interval schedule in Cohort 2b.
- 70% of active vaccine recipients in the 28-day interval schedule (75% for placebo) and 72% of active vaccine recipients in the 56-day interval schedule (64% for placebo) in Cohort 3.

Post-hoc analyses did not indicate any obvious effect of Ad26 VNA titers on the immunogenicity of the regimens at 21 days post dose 2 (data not shown in this Synopsis).

#### STUDY LIMITATIONS:

A total of 259 participants in Cohort 1 either did not receive dose 2 (N=52) or received dose 2 outside of their protocol-defined interval (N=207), mainly due to the study pause, resulting in a reduced precision for the immunogenicity estimates in the Per Protocol Analysis Set. Unfortunately due to PBMC shipment losses, less children, adolescents and HIV-infected participants were analyzed for cellular immune responses than originally planned.

#### CONCLUSION:

The 2-dose heterologous vaccination regimens in this study using Ad26.ZEBOV at  $5 \times 10^{10}$  vp as the first dose and MVA-BN-Filo at  $1 \times 10^8$  Inf.U as the second dose were well-tolerated and no safety concerns were identified in any of the study cohorts. Overall, adverse events reported post vaccination were mild in the majority of participants and transient in nature. No deaths or serious adverse events considered to be related to study vaccine were reported. There were no IREs, and only 1 participant did not receive the dose 2 vaccination due to an adverse event (second-degree burns due to a domestic accident). There was no apparent influence of the time interval between the Ad26.ZEBOV and MVA-BN-Filo doses (ie, 28, 56 or 84 days, or up to 483 days mainly due to the study pause) on the occurrence of adverse events.

The 2-dose heterologous regimens in this study induced robust binding antibody responses at 21 days post dose 2 in 98% to 100% of HIV-uninfected adult and elderly participants in Cohort 1 (aged 18-70 years), in 100% of HIV-infected adult participants in Cohorts 2a (aged 18-50 years), and in 100% of adolescents (aged 12-17 years) and children (aged 4-11 years) in Cohort 2b and Cohort 3, respectively. In HIV-uninfected participants (adults, elderly, adolescents, and children), extending the time interval between dose 1 and dose 2 from 28 days to 56 days resulted in higher binding antibody levels at 21 days post dose 2. In HIV-infected participants, similar binding antibody GMCs were observed for the 28-day and 56-day interval at 21 days post dose 2. Further extension of the interval from 56 days to 84 days (evaluated in Cohort 1 only) did not yield further increases in binding antibody concentrations. At 1 year post dose 1, the binding antibody levels were similar across the 28-, 56- and 84-day interval schedules and lower compared to 21 days post dose 2.

No relevant differences were observed between the binding antibody responses in HIV-infected adults and those in HIV-uninfected adults and elderly. The binding antibody responses observed in adolescents and children were higher than those observed in HIV-uninfected adult and elderly participants.

Based on a sensitivity analysis in HIV-uninfected adult and elderly participants in Cohort 1, there is no indication that a delay in dose 2 vaccination up to 483 days post dose 1 negatively impacted vaccine-induced binding antibody responses. Similarly, delaying the booster dose beyond 30 days of Day 365 post dose 1 did not negatively impact binding antibody responses.

A correlation analysis performed between baseline and 21 days post dose 2 binding antibody concentrations did not indicate an obvious positive (anamnestic response) or negative (immune interference) effect of the baseline ELISA values on the immunogenicity.

The 2-dose regimens also induced robust neutralizing antibody responses (evaluated in Cohort 1 only). At 21 days post dose 2 and 1 year post dose 1, a strong positive correlation was observed between the binding antibody concentrations and neutralizing antibody titers, indicating that most of the vaccine-induced EBOV GP-specific binding antibodies also have neutralizing function.

EBOV GP-specific CD4<sup>+</sup> T-cell responses (ICS) were observed in a substantial amount of participants 21 days post dose 2 for both the 28- and 56-day intervals. The median CD4<sup>+</sup> T-cell response at 21 days post dose 2 tended to be higher in participants vaccinated with the 28-day interval compared to those in the 56 day interval. Limited EBOV GP-specific CD8<sup>+</sup> T-cell responses (ICS) and IFN- $\gamma$  producing T-cell responses (IFN- $\gamma$  ELISpot) were detected at 21 days post dose 2 in participants vaccinated in either the 28- or 56 day interval. No apparent differences in cellular immune responses were observed between HIV-infected and HIV-uninfected adults. Taking into account the relatively small group sizes, no apparent differences in cellular immune responses were observed between adolescents, children, and healthy adults.

Furthermore, in a subset of 30 participants assigned the Ad26,MVA 56-day interval regimen in Cohort 1, the regimen induced SUDV GP-specific binding antibody responses in the majority of participants (87%) at 21 days post-dose 2, as expected given the similarity between EBOV GP and SUDV GP. MARV GP-specific antibodies were detected in 1 participant at a low level.

Finally, the vaccination regimens established immune memory in all 73 HIV-uninfected adult and elderly participants in Cohort 1 who received a booster dose with Ad26.ZEBOV at 1 year post dose 1 (window: +3 months). This was evidenced by 100% of the participants mounting a strong anamnestic response, quantified as a 55-fold increase in binding antibody concentrations within 7 days after the Ad26.ZEBOV booster vaccination.

## SIGNATURES

**Signed by**

Cynthia Robinson

**Date**

03Oct2019, 18:16:44 PM, UTC

**Justification**

Document Approval

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