Amsterdam, 20 July 2023
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

ZABDENO

Ebola vaccine (Ad26.ZEBOV-GP [recombinant])

Procedure no: EMEA/H/C/005337/P46/009

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 05 May 2023, the MAH submitted a completed paediatric study EBL2005 for Mvabea and Zabdeno, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The results of the primary analysis, which was performed when all participants had completed the 12-month post-Dose 1 visit or discontinued earlier (i.e. completed the main study phase), were submitted to EMA on 13 January 2023 as part of a grouped application comprising 3 Type II variations (EMEA/H/C/005343/II/0018/G for Mvabea and EMEA/H/C/005337/II/0015/G for Zabdeno).

This Article 46 submission contains the results of the final analysis, when all participants in the extension phase (i.e. vaccination of active control group with Ad26.ZEBOV, MVA-BN-Filo) had completed the 28 days post-Dose 2 visit or discontinued earlier.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study EBL2005 is a stand-alone study

2.2. Information on the pharmaceutical formulation used in the study

The following Ebola vaccines were given as a 0.5-mL IM injection:

- Ad26.ZEBOV: $5x10_{10}$ vp
- MVA-BN-Filo: $1x10_{8}$ Inf U

No specific paediatric pharmaceutical formulation is used.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study EBL2005

Study EBL2005 is a randomised, active-controlled, double-blind Phase 2 study conducted in Guinea (1 site) and Sierra Leone (1 site) to evaluate the safety, reactogenicity, and immunogenicity of the 2-dose heterologous regimen with Ad26.ZEBOV at a dose of $5x10^{10}$ vp followed by MVA-BN-Filo at a dose of $1x10^{8}$ Inf U administered 56 days later, in healthy infants aged 4-11 months (i.e. ≥4 months up to <12 months) versus an active control vaccine (MenACWY, MenACWY). The planned total sample size was approximately 107 infants, randomised to Ebola vaccines (Ad26.ZEBOV, MVA-BN-Filo) or active control vaccine in a blinded fashion. Approximately equal numbers of participants were to be enrolled in each country. Within each country, there was stratification by age group (i.e. 4-8 months, and 9-11 months of age). The results of the primary analysis, which was performed when all participants had completed the 12-month post-Dose 1 visit or discontinued earlier (i.e. completed the **main study phase**), were submitted to EMA on 13 January 2023 as part of a grouped application comprising 3 Type II variations (EMEA/H/C/005343/II/0018/G and EMEA/H/C/005337/II/0015/G) and is currently under review. The results of the final analysis, when all participants in the **extension phase** (i.e.

vaccination of active control group with Ad26.ZEBOV, MVA-BN-Filo) had completed the 28 days post-Dose 2 visit or discontinued earlier, are included in the current Article 46 submission.

In the current procedure, the new safety data from the extension phase is discussed. The safety and immunogenicity data obtained in the main study phase is discussed elsewhere (EMEA/H/C/005343/II/0018/G).

2.3.2. Clinical study EBL2005

Description

Methods

Study participants

The target population consisted of healthy infants aged ≥4 months up to <12 months who had received all routine immunisations appropriate for their age. Participants with a known allergy or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine products, with a history of EVD or prior exposure to EBOV were not eligible for entry in the study.

Treatments

Participants were randomised to receive Ad26.ZEBOV (first vaccination) at a dose of $5x10^{10}$ viral particles (vp) followed by MVA-BN-Filo (second vaccination) at a dose of $1x10^{8}$ infectious units (Inf U) or 2 doses of Meningococcal Group A, C, W135, and Y conjugate vaccine MenACWY (*Nimenrix)*.

Objectives and Endpoints

The **safety objective**, for which results are presented, is:

- To assess the safety and reactogenicity of the selected 2-dose heterologous vaccine regimen utilising Ad26.ZEBOV at a dose level of $5x10^{10}$ vp as Dose 1 and MVA-BN-Filo at a dose level of $1x10^{8}$ Inf U as Dose 2 after each dose.

Summaries of adverse events (AEs) and other safety data are based on the Full Analysis Set (FAS). The FAS included all participants who received at least 1 dose of study vaccine, regardless of the occurrence of protocol deviations. Data is reported separately for the main study phase and the extension phase.

AEs were collected as follows:

- Solicited local and systemic AEs (reactogenicity) from the day of vaccination until 7 days after each vaccination. Participants were provided with a diary to record solicited signs and symptoms of local and systemic AEs in the evening after each vaccination and then daily for the next 7 days. The investigator or his/her designee documented any AEs in the case report form.
- Solicited local AEs: injection site erythema, pain, and/or swelling.
- Solicited systemic AEs: pyrexia (body temperature ≥38°C). Pyrexia was graded as follows: Grade 1 = 38.0 to 38.4°C; Grade 2 = 38.5 to 38.9°C; Grade 3 = 39.0 to 40.0°C; and Grade 4 = >40.0°C.
- Unsolicited AEs from the day of vaccination until 28 after each vaccination.

- Serious adverse events (SAEs), including deaths, adverse events of special interest (AESIs; see below), and AEs leading to discontinuation were collected from signing of the informed consent form (ICF) onwards until the database lock for the respective analysis.
- Adverse Events of Special Interest (AESI): TTS has been observed very rarely following vaccination with Janssen COVID vaccine. TTS is a syndrome characterised by a combination of both a thrombotic event and thrombocytopenia. Because this syndrome is rare and not completely understood, all cases of thrombosis and/or symptomatic thrombocytopenia or thrombocytopenia were considered a potential case of TTS and had to be reported to the sponsor within 24 hours of awareness. Each potential event was to be reviewed to identify a TTS case.

Of note, laboratory, vital signs, and physical examination abnormalities that were considered to be clinically significant in the opinion of the investigator were to be reported as medical history if onset was prior to first vaccination and as AEs if onset was post-first vaccination.

Assessment of causality

Adverse drug reactions (ADRs) are defined as AEs for which a causal relationship between vaccination with the Ad26.ZEBOV, MVA-BN-Filo regimen and its occurrence is reasonably established, based on comprehensive assessment of the available AE information.

Solicited local AEs were considered as related to the study vaccine by definition. Solicited systemic and unsolicited AEs were considered related to the use of the study vaccine as per investigator assessment if the attribution was possibly, probably, or definitely related, and considered unrelated if the attribution was unrelated or doubtfully related.

The considerations for determination whether or not an AE was an ADR:

- Frequency ≥2x higher than control → ADR
- Frequency similar as in control, known ADR for control → ADR
- Frequency < control, no ADR unless medical reason to include
- Individual case suggestive of ADR → ADR

Randomisation and blinding (masking)

All participants were centrally assigned to randomised study vaccination using an IWRS.

The main phase of the study was a double-blind design. The extension phase for participants enrolled in the control arm of the main study, will be open label.

Statistical Methods

The sample size was not based on formal hypothesis testing considerations. This study expanded the safety and immunogenicity database for VAC52150 to infants.

Safety data were analysed descriptively for participants receiving Ebola vaccines or active control. Descriptive statistics were calculated for continuous immunologic parameters at all available time points. Frequency tabulations were calculated for discrete (qualitative) immunologic parameters as applicable.

Results

Participant flow

One hundred and eight (76.1%) out of the 142 participants screened for the study, were enrolled/randomised, and received the Ebola vaccines or the active control, 34 (23.9%) were screen failures, 31 failed to comply with eligibility criteria, 2 participants were withdrawn by parent or guardian, and 1 was withdrawn due to a physician's decision.

In the extension phase, 26 of 29 participants screened for the extension phase were enrolled and received the first dose of the Ebola vaccines (Ad26.ZEBOV), 3 did not meet the eligibility criteria. Of these, a total of 25 (96.2%) participants received the second dose of the Ebola vaccines (MVA-BN-Filo) and completed the extension phase. One (7.1%) participant in the 9-to-11-months stratification group prematurely terminated the study and discontinued Ebola vaccination due to an AE which excluded the participant from the second vaccination.

Table 1: Study Disposition; Extension phase, Full Analysis Set (Study VAC52150EBL2005)

	Ad26.ZEBOV, MVA-BN-Filo		
	4-8 Months	9-11 Months	4-11 Months Pooled
Analysis set: Full Analysis Set	12	14	26
Subjects ongoing	0	0	0
Completed study participation	12 (100.0%)	13 (92.9%)	25 (96.2%)
Terminated study participation prematurely	0	1 (7.1%)	1 (3.8%)
Reason for termination			
Adverse event	0	1 (100.0%)	1 (100.0%)

Restricted to subjects of the control arm during the main study, who received at least 1 dose of the active regimen during the extension phase.

[tsids02e.rtf] [Events/ds/pgm/ds02.sas] 17NOV2022, 3:35:23PM SAS 9.4

Recruitment

The study was conducted in 2 countries in Africa: 1 site in Guinea and 1 site in Sierra Leone.
Study Initiation Date: 19 August 2019; Study completion: 22 September 2022.

Baseline data

The demographic and baseline characteristics were comparable across vaccination groups. A higher proportion of participants were male (53.7%) and black (50.9%) (for 49.1% of participants, race was not reported). The median age was 7 months (range 4 to 11 months), the mean (standard deviation [SD]) weight-for-age was 40.8 (28.51) (Table 2).

Table 2: Summary of Demographics and Baseline Characteristics; Full Analysis Set (Study VAC52150EBL2005)

	Ad26.ZEBOV, MVA-BN-Filo			MenACWY, MenACWY			
	4-8 Months	9-11 Months	4-11 Months Pooled	4-8 Months	9-11 Months	4-11 Months Pooled	All Subjects
Analysis set: Full Analysis Set	43	32	75	19	14	33	108
Age, months							
N	43	32	75	19	14	33	108
Mean (SD)	5.7 (1.08)	10.4 (0.61)	7.7 (2.51)	5.4 (1.07)	10.4 (0.63)	7.5 (2.66)	7.6 (2.55)
Median	6.0	10.0	7.0	5.0	10.0	7.0	7.0
Range	(4; 7)	(9; 11)	(4; 11)	(4; 7)	(9; 11)	(4; 11)	(4; 11)
4 to <= 8 months	43 (100.0%)	0	43 (57.3%)	19 (100.0%)	0	19 (57.6%)	62 (57.4%)
>8 to 11 months	0	32 (100.0%)	32 (42.7%)	0	14 (100.0%)	14 (42.4%)	46 (42.6%)
Sex							
N	43	32	75	19	14	33	108
Female	19 (44.2%)	18 (56.3%)	37 (49.3%)	5 (26.3%)	8 (57.1%)	13 (39.4%)	50 (46.3%)
Male	24 (55.8%)	14 (43.8%)	38 (50.7%)	14 (73.7%)	6 (42.9%)	20 (60.6%)	58 (53.7%)
Race							
N	43	32	75	19	14	33	108
Black	25 (58.1%)	11 (34.4%)	36 (48.0%)	13 (68.4%)	6 (42.9%)	19 (57.6%)	55 (50.9%)
Not reported	18 (41.9%)	21 (65.6%)	39 (52.0%)	6 (31.6%)	8 (57.1%)	14 (42.4%)	53 (49.1%)
Ethnicity							
N	43	32	75	19	14	33	108
Hispanic or Latino	0	0	0	0	0	0	0
Not Hispanic or Latino	25 (58.1%)	11 (34.4%)	36 (48.0%)	13 (68.4%)	6 (42.9%)	19 (57.6%)	55 (50.9%)
Not reported	18 (41.9%)	21 (65.6%)	39 (52.0%)	6 (31.6%)	8 (57.1%)	14 (42.4%)	53 (49.1%)
Weight, kg							
N	43	32	75	19	14	33	108
Mean (SD)	7.3 (0.75)	8.5 (0.89)	7.8 (1.02)	7.6 (0.89)	8.2 (0.88)	7.9 (0.91)	7.8 (0.99)
Median	7.1	8.5	7.6	7.8	8.5	8.0	7.7
Range	(6; 9)	(7; 10)	(6; 10)	(6; 9)	(7; 10)	(6; 10)	(6; 10)
Height, cm							
N	43	32	75	19	14	33	108
Mean (SD)	65.6 (2.54)	72.8 (2.63)	68.7 (4.37)	66.1 (3.10)	72.1 (1.97)	68.7 (4.03)	68.7 (4.25)
Median	65.5	72.9	67.2	66.0	72.0	69.0	68.1
Range	(60; 72)	(66; 79)	(60; 79)	(60; 71)	(67; 75)	(60; 75)	(60; 79)
Weight-for-Age (4-11 months)							
N	43	32	75	19	14	33	108
Mean (SD)	40.4 (30.08)	38.2 (25.72)	39.5 (28.14)	55.3 (29.40)	28.4 (22.42)	43.8 (29.54)	40.8 (28.51)
Median	35.0	28.5	35.0	64.0	23.5	40.0	38.0
Q1; Q3	14.0; 63.0	15.0; 62.5	15.0; 63.0	33.0; 82.0	7.0; 38.0	19.0; 70.0	15.0; 64.0
Min; Max	2; 99	4; 81	2; 99	7; 94	3; 70	3; 94	2; 99
<3rd percentile	1 (2.3%)	0	1 (1.3%)	0	0	0	1 (0.9%)
>=3rd and <5th percentile	1 (2.3%)	1 (3.1%)	2 (2.7%)	0	2 (14.3%)	2 (6.1%)	4 (3.7%)
>=5th and <=95th percentile	39 (90.7%)	31 (96.9%)	70 (93.3%)	19 (100.0%)	12 (85.7%)	31 (93.9%)	101 (93.5%)
>95th and <=97th percentile	0	0	0	0	0	0	0
>97th percentile	2 (4.7%)	0	2 (2.7%)	0	0	0	2 (1.9%)

Note: N's for each parameter reflect non-missing values.
"Not reported" race and ethnicity: Local regulatory laws in Guinea did not permit investigators to collect data about race and ethnicity.
Source: modified from Attachment TSIDEM01 and Attachment TSIDEM02.

The baseline characteristics for the participants in the extension phase were comparable, except that there were relatively more male participants (61.5%) compared to female (38.5%).

Number analysed

The FAS in the extension phase existed of 26 patients.

Safety results

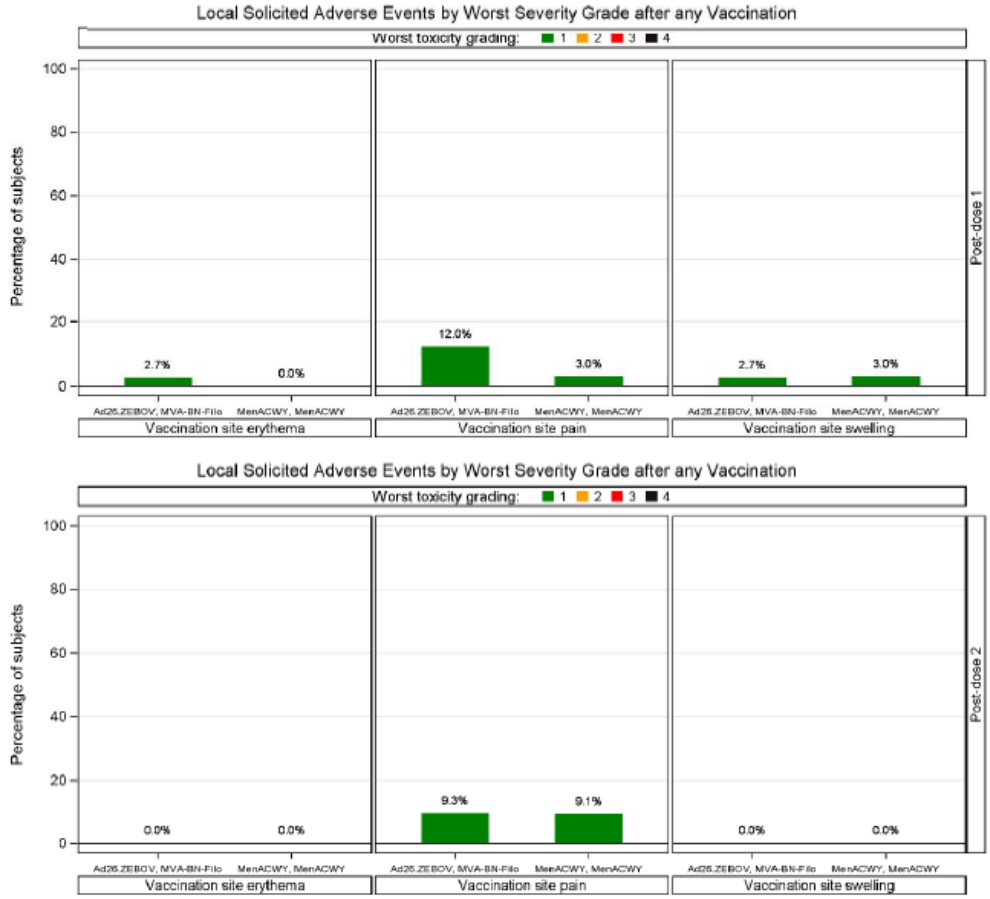
In general, the reactogenicity and safety profile of the Ebola vaccines (Ad26.ZEBOV, MVA-BNFilo) was comparable to what was observed during the main study phase.

Adverse events

Solicited AEs

In **the main phase**, solicited local AEs were reported by 22.7% of the participants who received Ebola vaccines (14.7% after Ad26.ZEBOV vaccination [Dose 1], and 9.3% after MVA-BN-Filo vaccination [Dose 2]) compared with 15.2% of those who received active control (Figure 1). The most frequently (at least 10% in any vaccination group) reported solicited local AE was transient vaccination site pain (in 20.0% in the Ebola vaccine group and 12.1% in the active control group). All solicited local AEs were Grade 1 in severity, with a median duration of 2 days.

Figure 1: Graphical Presentation of Local Solicited Adverse Events by Worst Severity Grade After Vaccination; Full Analysis Set (Study VAC52150EBL2005).



In the extension phase, solicited local AEs were reported by 34.6% of the participants (Table 3), 30.8% after Ad26.ZEBOV vaccination [Dose 1], and 16.0% after MVA-BN-Filo vaccination.

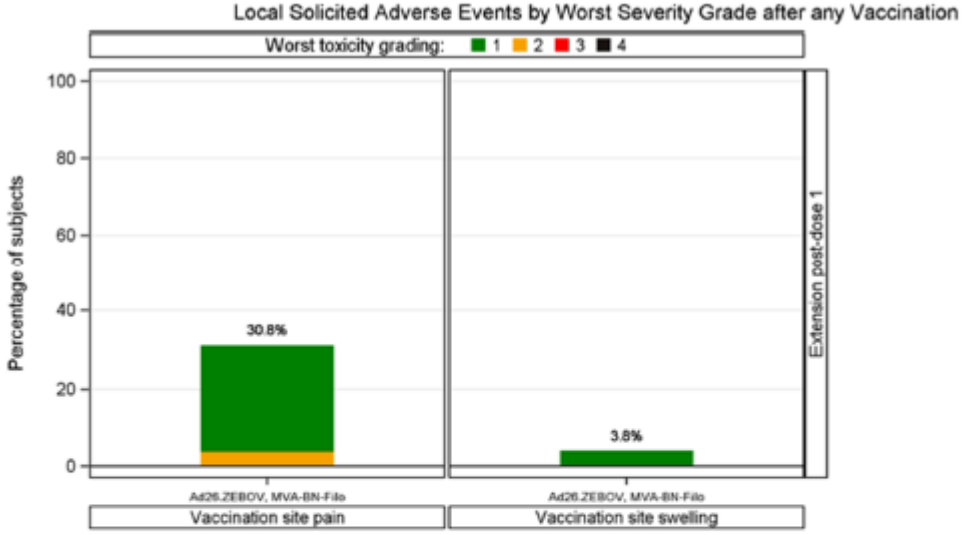
The most frequently (at least 10%) reported solicited local AE was vaccination site pain (34.6%) (*Figure 2*). The median time to onset of this event was 2 days, regardless of the study vaccination (Ad26.ZEBOV, MVA-BN-Filo). The median duration of this event was 1 day following Ad26.ZEBOV vaccination and 2.5 days following MVA-BN-Filo vaccination. The maximum observed duration of this event was 6 days, reported after Ad26.ZEBOV vaccination. All solicited local AEs were Grade 1 or 2 in severity.

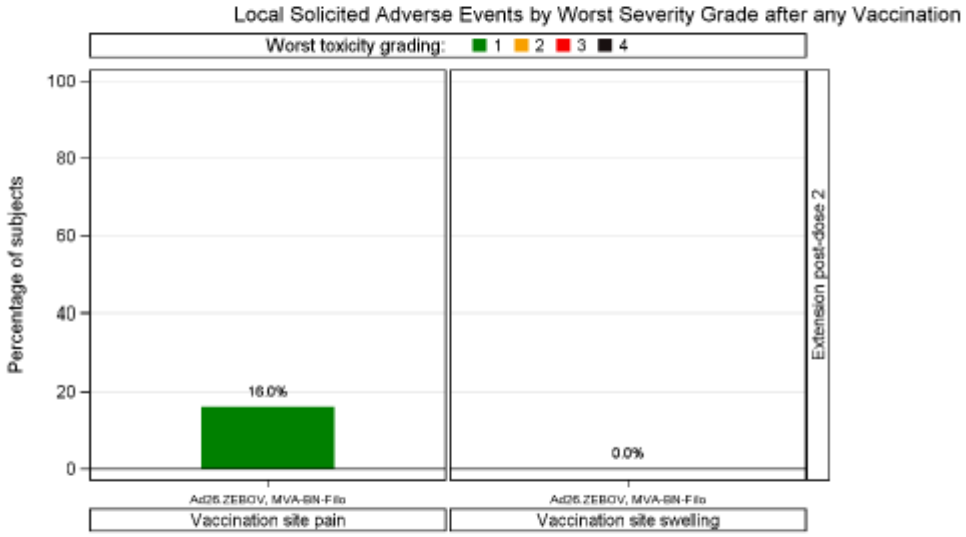
Table 3: Overall Summary of Solicited Adverse Events - Extension Phase; Full Analysis Set (Study VAC52150EBL2005

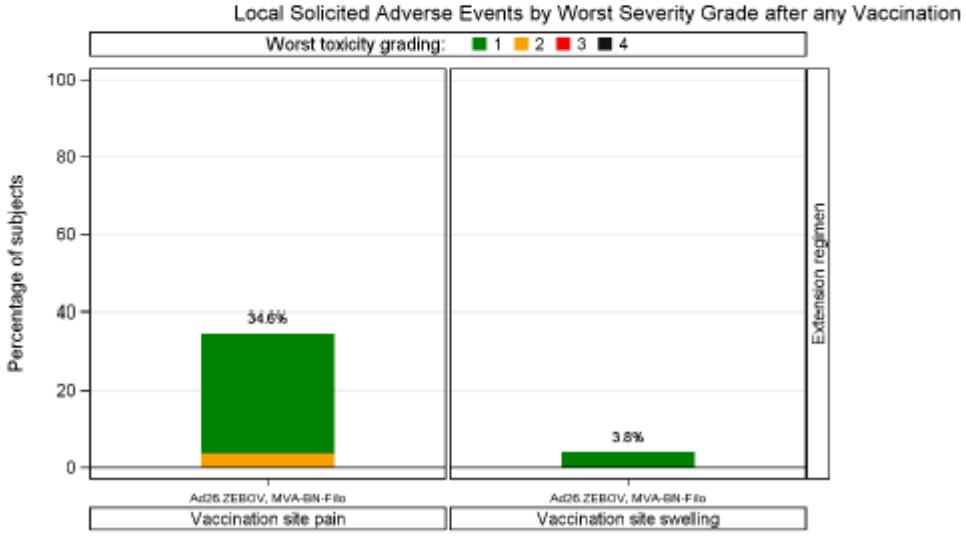
	Ad26.ZEBOV, MVA-BN-Filo		
	4-8 Months	9-11 Months	4-11 Months Pooled
Solicited systemic AE of at least grade 3 thought to be related to study vaccine	0	0	0
Extension Regimen	12	14	26
Subjects with 1 or more:			
Solicited AE	7 (58.3%)	11 (78.6%)	18 (69.2%)
Solicited AE of grade 1 & 2 as worst grade	7 (58.3%)	11 (78.6%)	18 (69.2%)
Solicited AE of grade 3 as worst grade	1 (8.3%)	0	1 (3.8%)
Solicited AE of grade 4 as worst grade	0	0	0
Solicited local AE	3 (25.0%)	6 (42.9%)	9 (34.6%)
Solicited local AE of grade 1 & 2 as worst grade	3 (25.0%)	6 (42.9%)	9 (34.6%)
Solicited local AE of grade 3 as worst grade	0	0	0
Solicited local AE of grade 4 as worst grade	0	0	0
Solicited systemic AE	5 (41.7%)	9 (64.3%)	14 (53.8%)
Solicited systemic AE of grade 1 & 2 as worst grade	5 (41.7%)	9 (64.3%)	14 (53.8%)
Solicited systemic AE of grade 3 as worst grade	1 (8.3%)	0	1 (3.8%)
Solicited systemic AE of grade 4 as worst grade	0	0	0
Solicited systemic AE thought to be related to study vaccine	4 (33.3%)	6 (42.9%)	10 (38.5%)
Solicited systemic AE of at least grade 3 thought to be related to study vaccine	0	0	0

Key: AE = adverse event
Note: Subjects are counted only once within a period for any given event, regardless of the number of times they actually experienced the event in that period. The same event in one subject in post-dose 1 and post-dose 2 will be counted once in the regimen phase.
Restricted to subjects of the control arm during the main study, who received at least 1 dose of the active regimen during the extension phase.

Figure 2: Graphical Presentation of Most Frequent Local Solicited Adverse Events by Worst Severity Grade after Vaccination - Extension Phase; Full Analysis Set (Study VAC52150EBL2005)







In **the main study phase** solicited systemic AEs were reported by 57.3% of the participants who received Ebola vaccines (36.0% after Ad26.ZEBOV vaccination [Dose 1], and 29.3% after MVA-BN-Filo vaccination [Dose 2]) compared with 54.5% of those who received active control. The most frequently (at least 10% in any vaccination group) reported solicited systemic AEs were irritability (34.7% in Ebola vaccine group and 30.3% in active control group), diarrhoea (17.3% and 24.2%), decreased appetite (24.0% and 21.2%), pyrexia (21.3% and 9.1%), decreased activity (20.0% and 15.2%), and vomiting (10.7% and 12.1%). Solicited systemic AEs were Grade 1 or Grade 2 in severity in the Ad26.ZEBOV/MVA-BN-Filo group. The median duration of the events was 1 to 2 days following Ad26.ZEBOV or MVA-BN-Filo vaccination, the maximum observed duration was 7 days, which was reported for irritability after Ad26.ZEBOV vaccination.

Pyrexia was more frequently (>10% difference) reported by participants who received Ebola vaccines compared with those who received active control (21.3% versus 9.1%).

In **the extension phase** Solicited systemic AEs were reported by 53.8% of the participants, 42.3% after Ad26.ZEBOV vaccination (Dose 1) and 32.0% after MVA-BN-Filo vaccination (Dose 2).

The most frequently (at least 10%) reported solicited systemic AEs were decreased activity (42.3%), decreased appetite (26.9%), pyrexia (23.1%), vomiting (15.4%), and irritability (11.5%). All frequent solicited systemic AEs were transient in nature. The median time to onset of the events ranged between 1 to 2 days following Ad26.ZEBOV vaccination and 4 to 6 days following MVA-BN-Filo vaccination. The median duration of the events was 1 day following Ad26.ZEBOV or MVA-BN-Filo vaccination. The maximum observed duration was 6 days, which was reported for decreased appetite after MVA-BN-Filo vaccination.

The majority of participants reported solicited systemic AEs with a worst grade severity of Grade 1 (50.0%). The only Grade 3 event was pyrexia, reported for a participant in the 4-to-8-month stratification group after MVA-BN-Filo vaccination, which was not considered to be related to the Ebola vaccine by the investigator. The Grade 3 pyrexia event started within 4 days following vaccination with MVA-BN-Filo, and the duration was 1 day.

Fever or pyrexia within 8 days of vaccination in the extension phase was reported by 26.9% of participants, 23.1% after Ad26.ZEBOV vaccination (Dose 1) and 8.0% after MVA-BN-Filo vaccination (Dose 2).

Four (15.4%) participants experienced Toxicity Grade 1 events of pyrexia after Ad26.ZEBOV vaccination (Dose 1), 1 (3.8%) experienced a Toxicity Grade 2 event of pyrexia after Ad26.ZEBOV vaccination (Dose 1), and 3 (11.5%) experienced Toxicity Grade 3 events of pyrexia (1 [3.8%] after Ad26.ZEBOV vaccination [Dose 1] and 2 [8.0%] after MVA-BN-Filo vaccination [Dose 2]).

There was 1 clinically significant vital sign abnormality of Grade 3 pyrexia after MVA-BN-Filo (Dose 2) vaccination (refer to Section 5.1.2.1.2 for details). The 6 other clinically significant vital sign abnormalities of pyrexia were Grade 1 in severity.

The percentage of participants with at least 1 related solicited systemic AE was 38.5%, 34.6% after Ad26.ZEBOV vaccination (Dose 1) and 16.0% after MVA-BN-Filo vaccination (Dose 2). The most frequent (at least 10%) related solicited systemic AEs were decreased activity (23.1%), decreased appetite (19.2%), and pyrexia (15.4%). Throughout the study, related cases of decreased activity, decreased appetite, and pyrexia were reported at a slightly higher rate (>10% difference) after Ad26.ZEBOV vaccination compared with MVA-BN-Filo vaccination.

Unsolicited AEs

In **the main phase**, unsolicited AEs (within 28 days of vaccine administration) were reported by 82.7% of the participants who received Ebola vaccines (61.3% after Ad26.ZEBOV vaccination [Dose 1], and 57.3% after MVA-BN-Filo vaccination [Dose 2]) compared with 84.8% of those who received active control. The most frequently (at least 10% in any vaccination group) reported unsolicited AEs by SOC were infections and infestations (80.0% in the Ebola vaccine group and 84.8% in the active control group); skin and subcutaneous tissue disorders (8.0% and 15.2%); and gastrointestinal disorders (12.0% and 3.0%). The most frequently (at least 10% in any vaccination group) reported unsolicited AEs by preferred term were respiratory tract infection (20.0% and 27.3%), malaria (17.3% and 27.3%), nasopharyngitis (17.3% and 18.2%), bronchitis (12.0% and 21.2%), rhinitis (13.3% and 15.2%), upper respiratory tract infection (10.7% and 18.2%), acrodermatitis (8.0% and 12.1%), and gastroenteritis (10.7% and 6.1%). None of the unsolicited AEs were considered to be related to the study vaccine by the investigator.

In **the extension phase**, unsolicited AEs (within 28 days of vaccine administration) were reported by 38.5% of the participants, 34.6% after Ad26.ZEBOV vaccination (Dose 1) and 28.0% after MVA-BN-Filo vaccination (Dose 2). One participant experienced an unsolicited AE (anemia) at follow-up 1. The event was Grade 1 in severity, non-serious, and considered not related to the study vaccine by the investigator.

The most frequently (at least 10%) reported unsolicited AEs by system organ class were infections and infestations (34.6%). The most frequently (at least 10%) reported unsolicited AEs by preferred term were malaria (23.1%), helminthic infection (11.5%), and upper respiratory tract infection (11.5%).

All unsolicited AEs (reported within 28 days of study vaccination) were resolving or resolved by the end of the study. No Grade 3 or Grade 4 unsolicited AEs were reported. There were no SAEs or unsolicited AEs (within 28 days of vaccine administration) leading to discontinuation of study vaccination.

None of the unsolicited AEs in the extension study phase were considered to be related to the study vaccine by the investigator.

Adverse Events of Special Interest

Thrombosis with Thrombocytopenia Syndrome: No AESIs including potential TTS cases were identified.

Serious adverse events and deaths, other significant events

There were no deaths during the study.

In **the main study phase**, a total of 25 SAEs (8 SAEs after Ad26.ZEBOV vaccination, 10 after MVA-BN-Filo vaccination, and 7 in the active control group) occurred in 14 participants throughout the study (including both follow-up periods; Table 4). Most of the SAEs in this study population were attributable to infections and infestations, the most frequent SAE by preferred term was gastroenteritis (reported for 6.7% in Ebola vaccine group and 3.0% in active control group). None of the SAEs were considered to be related to study vaccine by the investigator.

There were no SAEs in **the extension phase**.

Laboratory findings

In the **main study phase**, a total of 11 clinically significant laboratory abnormalities were observed in 8 participants (4 participants in the Ebola vaccine group and 4 in the active control group). Of these, there were seven events of clinically significant low haemoglobin (includes 4 at screening; 3 post-vaccination in the Ad26.ZEBOV/MVA-BN-Filo group), two events of clinically significant low erythrocytes at screening, one event of clinically significant grade 2 low haematocrit post-Dose 2 in the

Ad26.ZEBOV, MVA-BN-Filo group and 1 event of clinically significant Grade 2 low platelets (50,000 to 74,999/m³) at follow-up 1 (Day 57 Visit) in the active control group were reported. The Grade 2 event of low platelets was an isolated, asymptomatic event and was not associated with a thrombotic event.

In the **extension phase**, Two events of clinically significant low haemoglobin in 2 participants were observed, both had Toxicity Grade 2 low haemoglobin at follow-up 1 (Extension Day 57 Visit). No other clinically significant laboratory abnormalities were observed during the extension phase.

Discontinuations

There were no AEs leading to study or study vaccine discontinuation in the main study phase.

One participant in the 9-to-11-months stratification group discontinued study vaccination and the study due to an AE (anemia) at follow-up 1 of the extension phase. The event was Grade 1 in severity, non-serious, and considered not related to the study vaccine by the investigator.

2.3.3. Discussion on clinical aspects

No efficacy or effectiveness data is available for the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen. Clinical benefit has been inferred by bridging the EBOV GP-binding antibody response as observed in humans (adults) approximately 21 days after the second dose to the EBOV GP-binding antibody response observed in NHPs approximately 21 days after the second dose (see EPAR for more details).

Immunogenicity data in infants 4-11 months of age has been discussed in the ongoing type 2 variation and is thus not discussed here.

The safety objective, for which results are presented is:

- To assess the safety and reactogenicity of the selected 2-dose heterologous vaccine regimen utilising Ad26.ZEBOV at a dose level of $5x10^{10}$ vp as dose 1 and MVA-BN-Filo at a dose level of $1x10^{8}$ Inf U as dose 2 after each dose.

Safety data from the main study phase have also been assessed in the ongoing type 2 variation but are presented for completeness and to enable comparison of the safety data obtained in the extension phase with that in the main study phase.

Exposure

Safety data is available for 75 infants receiving the Ebola vaccine regimen in the main study phase and from 26 in the extension phase. Of the 33 infants in the control arm in the main study phase, 29 were screened for enrollment in the extension phase, and 26 were enrolled and received the Ebola vaccines. Screen failures were recorded as not meeting the criteria "Infant must be healthy in the investigator's clinical judgment". It is conceivable in the study population that health status changes from the main study period to the extension phase.

Reactogenicity

In the extension phase, solicited local AEs were reported by 34.6% of the participants, 30.8% after Ad26.ZEBOV vaccination [Dose 1], and 16.0% after MVA-BN-Filo vaccination. This is relatively high compared to the 20% reported for injection site pain in the Ebola group in the main study phase. This is not discussed by the applicant, and the reason is unknown. As there is no control arm in the extension phase, as no information is provided on the reporting of reactions in these participants in the study, and as the sample size is relatively limited, no firm conclusions can be drawn other than that the reactogenicity does not seem drastically different or worse following Ad26.ZEBOV vaccination in the extension phase versus the main study phase.

The frequency of solicited systemic AEs was similar in the extension phase compared to the main phase of the study. Solicited systemic AEs were reported by 53.8% of the participants, 42.3% after Ad26.ZEBOV vaccination (Dose 1) and 32.0% after MVA-BN-Filo vaccination (Dose 2) in the extension phase compared to 57.3% of the participants who received Ebola vaccines (36.0% after Ad26.ZEBOV vaccination [Dose 1], and 29.3% after MVA-BN-Filo vaccination [Dose 2]) in the main study phase.

Pyrexia was more frequently reported in the extension phase (26.9%) versus the main study phase (21.3%) but is not considered a relevant difference.

The majority of participants reported solicited systemic AEs with a worst grade severity of Grade 1 (50.0%). The only Grade 3 event was pyrexia, reported for a participant in the 4-to-8-month stratification group after MVA-BN-Filo vaccination, which was not considered to be related to the Ebola vaccine by the investigator. As the Grade 3 pyrexia event started within 4 days following vaccination with MVA-BN-Filo, a causal relationship cannot be excluded. Pyrexia is a known ADR for Mvabea.

Unsolicited AEs

In infants enrolled in EBL2005, unsolicited AEs reported mostly concerned infections occurring in ~60% of participants within 28 days of dose 1 and dose 2. Unsolicited AEs were not considered related to vaccination by investigators. This can be agreed. In the extension phase, 38.5% of the participants experienced an unsolicited AE; 34.6% after Ad26.ZEBOV vaccination (Dose 1) and 28.0% after MVA-BN-Filo vaccination. This is lower than in the main study phase.

Deaths and SAEs

There were no deaths. In the main study phase, SAEs were reported in 10 infants (13%) in the active vaccine group and 4 infants (12%) in the control group. SAEs were mostly attributable to the SOC Infections and infestations. None were considered related to vaccine. In the extension phase of the study, there were no SAE's.

Laboratory findings

Clinical laboratory evaluations do not give rise to any relevant signals; findings are in line with the study population where there is a relatively high incidence of infectious diseases including malaria. The observations of low haemoglobin in the extension phase are in line with the main study phase.

There was one AE leading to study or study vaccine discontinuation, which was a case of anemia at follow-up 1 of the extension phase. The event was Grade 1 in severity, non-serious, and considered not related to the study vaccine by the investigator. This is agreed as the event occurred 100 days after the first dose of the Ebola regimen (Ad26.ZEBOV).

Conclusion

In conclusion, the safety data for the heterologous two dose priming regimen in the extension phase is in line with the observed safety profile of Ad26.ZEBOV and MVA.BN.Filo in the main part of the study and overall, is in line with the known safety profile in children >1 year of age. The available safety data in infants aged 4 to 11 months inclusive does not raise any concerns, but data is limited to 101 infants exposed to the Ad26.ZEBOV, MVA.BN.Filo regimen (75 in the main study phase and 26 from the extension phase).

3. Rapporteur's overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.