Maternal safety, reactogenicity, and immunogenicity of a 2-dose Ebola vaccine regimen in healthy pregnant women

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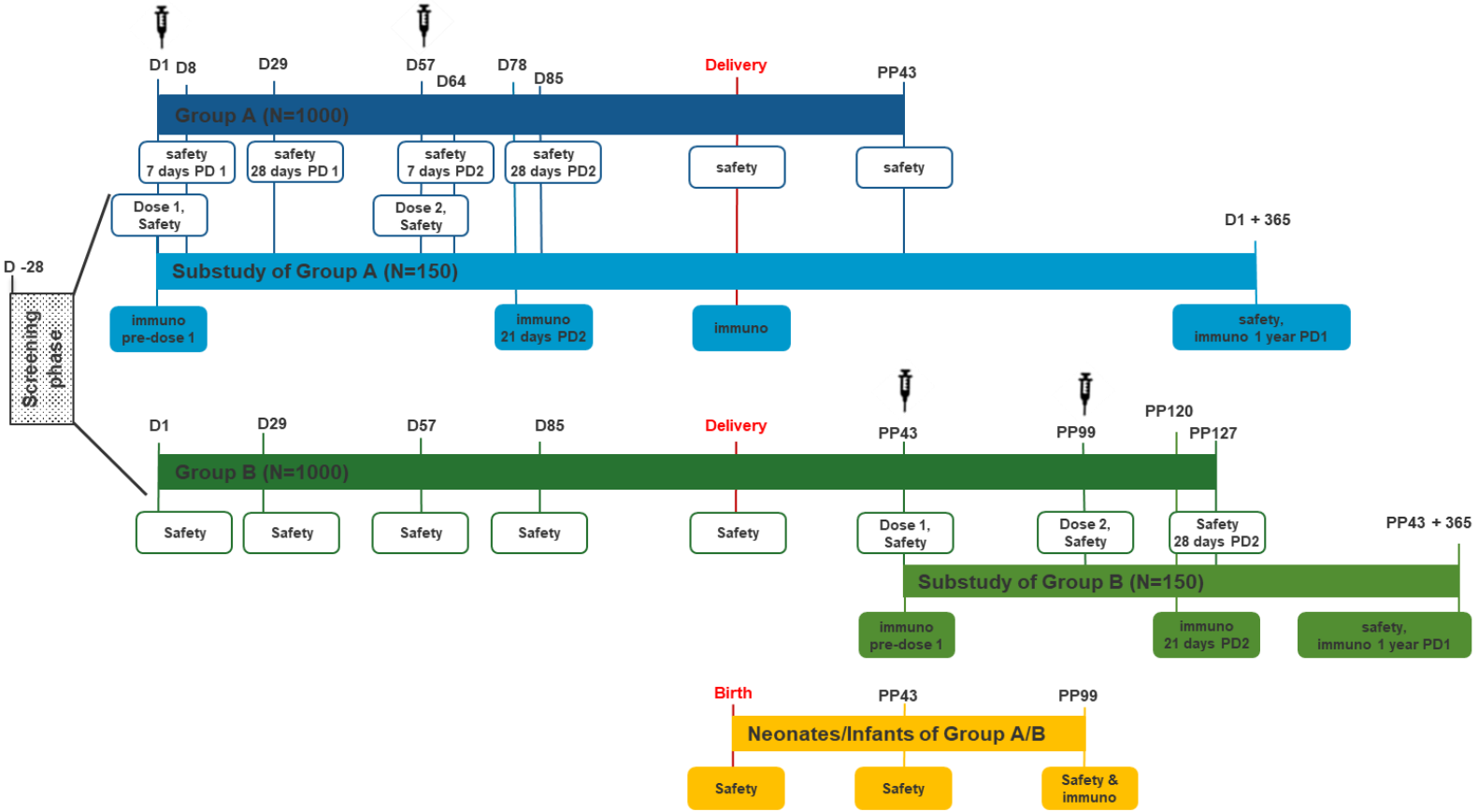
Background/Rationale

- Risks to mother and fetus following Ebola virus disease (EVD) are very high, with case fatality rate in pregnant women infected with EVD ranging from 53% to 89%.

- The Janssen 2-dose Ebola vaccine regimen, composed of Ad26.ZEBOV **(Zabdeno®)** administered on Day 1 and MVA-BN-Filo **(Mvabea®)** administered after 56 days, has been widely tested for safety and approved for prevention of EVD in non-pregnant populations ≥ 1 year of age.

We conducted an assessment of safety and immunogenicity of the 2-dose Ebola vaccine regimen to support use of the vaccines in pregnant women.

Schematic overview of the study design



Trial Objectives

Primary

- Assess adverse **maternal/fetal outcomes** of the 2-dose Ebola vaccine regimen **during pregnancy**.
- Assess adverse **neonatal/infant outcomes** of the 2-dose Ebola vaccine regimen in neonates/infants

Secondary

- Assess the **safety** of the 2-dose Ebola vaccine regimen in pregnant women
- Assess the **safety** of the 2-dose Ebola vaccine regimen in neonates/infants
- Assess the **reactogenicity and unsolicited AEs** of the 2-dose Ebola vaccine regimen during pregnancy
- Assess the **immunogenicity** of the 2-dose Ebola vaccine regimen among pregnant and non-pregnant women
- Assess **persistence of maternal antibodies in infants** born to women who received the 2-dose Ebola vaccine regimen during pregnancy

Primary endpoints

Maternal Outcomes

- Spontaneous abortion
- Stillbirth
- Pre-eclampsia/eclampsia
- Antenatal bleeding
- Pathways to preterm birth (premature preterm rupture of membranes, preterm labor, insufficient cervix, provider initiated preterm birth)
- Post-partum hemorrhage
- Maternal death

Neonatal outcomes

- Congenital anomalies
- Small for gestational age (SGA)
- Low birth weight
- Preterm birth
- Failure to thrive
- Neonatal death

Enrolment and demographics

- Screened: **3484**, enrolled and vaccinated: **1964** (Group A=992 vs Group B=972)
- Live birth: **1945** infants
- Enrolled in Immunogenicity sub-study: **329** (Group A=161 vs Group B=168)
- Overall, demographic characteristics were comparable in mothers between group A and B.

	Group A	Group B	All Participants
N	992	1020	2012
Age, years Median (Q1; Q3)	26.0 (22.0; 30.0)	26.0 (22.0; 30.0)	26.0 (22.0; 30.0)
Age, years			
18-25	491 (49.5%)	496 (48.6%)	987 (49.1%)
26-50	501 (50.5%)	524 (51.4%)	1025 (50.9%)
>50	0	0	0
Race: Black or African American	992 (100.0%)	1020 (100.0%)	2012 (100.0%)
Weight, kg (Median (Q1; Q3)	59.20 (54.05; 64.95)	59.00 (54.00; 65.20)	59.10 (54.00; 65.00)
Height, cm (Median (Q1; Q3)	158.0 (155.0; 162.0)	158.0 (155.0; 163.0)	158.0 (155.0; 163.0)
HIV infection status			
Negative	987 (99.5%)	1009 (98.9%)	1996 (99.2%)
Positive	5 (0.5%)	11 (1.1%)	16 (0.8%)

Maternal Safety data

Number and Percentage of Maternal/Fetal Outcomes of Special Interest, from randomization to 6 weeks postpartum – Primary Endpoints

	Group A	Group B
N	977	1000
Participants with any outcome	51 (5.2%)	73 (7.3%)
Maternal death	0	0
Spontaneous abortion	4 (0.4%)	5 (0.5%)
Stillbirth	9 (0.9%)	14 (1.4%)
Pre-eclampsia/eclampsia	4 (0.4%)	11 (1.1%)
Antenatal bleeding	4 (0.4%)	5 (0.5%)
Postpartum hemorrhage	7 (0.7%)	11 (1.1%)
Pathways to preterm birth	31 (3.2%)	34 (3.4%)

- **Overall**, the percentages of women with **any outcome** for Group A total and Group B total are **comparable** (5.2% versus 7.3%).

Summary of Serious Adverse Events (SAEs)

	Group A	Group B
N	**992**	**1020**
Participants with 1 or more		
SAE	**97 (9.8%)**	**92 (9.0%)**
SAE considered to be related to study vaccine	**4 (0.4%)**	**0**
AE with fatal outcome	**0**	**1 (0.1%)**

- SAE considered to be related to study vaccine
  - One participant (Group A) had **vomiting** and **nausea** that occurred on the same day of Dose 1 with duration of 2 days.
  - One participant (Group A) had **pyrexia** and **headache** that occurred one day after Dose 2 with duration of 1 day and 3 days, respectively.
  - One participant (Group A) had **fatigue** that occurred one day after Dose 1 with duration of 9 days.
  - One participant (Group A) had **fatigue** that occurred two days after Dose 1 with duration of 5 days.
- AE with fatal outcome
  - One participant (Group B) had **crush injury** that occurred 19 days after receiving Dose 1.

- **Overall**, the percentages of women with **1 or more SAEs** are **comparable** between Group A and Group B.

Summary of Reactogenicity for Group A

	Post-dose 1	Post-dose 2	Regimen
	Total	Total	Total
N	992	981	992
Participants with 1 or more:			
Solicited AE	556 (56.0%)	425 (43.3%)	637 (64.2%)
Solicited AE of worst grade 3	15 (1.5%)	6 (0.6%)	21 (2.1%)
Solicited local AE	364 (36.7%)	275 (28.0%)	461 (46.5%)
Solicited local AE of worst grade 3	2 (0.2%)	1 (0.1%)	3 (0.3%)
Solicited systemic AE	475 (47.9%)	342 (34.9%)	562 (56.7%)
Solicited systemic AE of worst grade 3	13 (1.3%)	5 (0.5%)	18 (1.8%)

- **Overall**, the percentages of women who experienced **solicited AEs (local and systemic AEs)** are **higher** after Dose 1 (Ad26.ZEBOV) than after Dose 2 (MVA-BN-Filo).
- Percentages of women with **solicited AEs of at least grade 3** are **comparable** between the two doses.
- No grade 4 solicited AE reported in the trial

Summary of Unsolicited Adverse Events (AEs)

	Post-dose 1		Post-dose 2		Regimen	
	Group A Total	Group B Total	Group A Total	Group B Total	Group A Total	Group B Total
N	992	972	981	963	992	972
Participants with 1 or more:						
Unsolicited AE	338 (34.1%)	56 (5.8%)	311 (31.7%)	91 (9.4%)	522 (52.6%)	139 (14.3%)
Unsolicited AE of worst grade 3	7 (0.7%)	1 (0.1%)	6 (0.6%)	0	13 (1.3%)	1 (0.1%)
Unsolicited AE considered to be related to study vaccine	97 (9.8%)	2 (0.2%)	69 (7.0%)	0	149 (15.0%)	2 (0.2%)
AE leading to discontinuation of study vaccine	0	1 (0.1%)	0	0	0	1 (0.1%)

- **Overall**, the percentages of women who experienced **unsolicited AEs**, as well as the percentages of women who experienced **unsolicited AEs considered to be related to the study vaccine**, appear **higher** for Group A compared to Group B during both the post-dose 1 (Ad26.ZEBOV) and post-dose 2 (MVA-BN-Filo) periods, as well as the regimen phase.
- However, study design **does not permit a direct comparison** of post dose unsolicited AEs between pregnant (Group A) and post-partum (Group B) women.
- Also, **Group A had more frequent scheduled interactions** during the 28-day window for collecting unsolicited adverse events than Group B.
- Occurrence of unsolicited AEs from the Summary of Clinical Safety is *comparable* to occurrence in Group A women
- No grade 4 unsolicited AEs were reported during the trial

Most Frequent Unsolicited Adverse Events

	Group A	Group B
N	992	1020
Post-dose 1	992	972
Participants with 1 or more Unsolicited AEs	338 (34.1%)	56 (5.8%)
Headache	83 (8.4%)	5 (0.5%)
Nasopharyngitis	53 (5.3%)	1 (0.1%)
Nausea	47 (4.7%)	0
Abnormal uterine bleeding	0	5 (0.5%)
Back pain	27 (2.7%)	4 (0.4%)

- **Post-dose 1**, the percentages of women with **unsolicited AEs** appear **higher** for Group A total compared to Group B total (34.1% vs 5.8%). Same pattern observed **post-dose 2.**
- However, study design **does not permit an equitable comparison** of post dose unsolicited AEs between pregnant (Group A) and post-partum (Group B) women.
- The top 3 AEs in Group A are events that are usually **observed during pregnancy**.

Infants safety data

Number and Percentage of Infants with Neonatal/Infant Outcomes of Special Interest – Primary Endpoints

	Group A	Group B
Birth to 14 weeks of age		
N	964	981
Participants with any outcome	**251 (26%)**	**251 (25.6%)**
Neonatal death	11 (1.1%)	5 (0.5%)
Congenital anomaly	9 (0.9%)	11 (1.1%)
Failure to thrive	87 (9.0%)	101 (10.3%)
Low birth weight	45 (4.7%)	49 (5.0%)
Small for gestational age	138 (14.3%)	116 (11.8%)
Preterm birth	26 (2.7%)	30 (3.1%)

- **Overall**, the percentages of infants with **any outcome** are **comparable** between Group A total and Group B total (26.0% versus 25.6%).

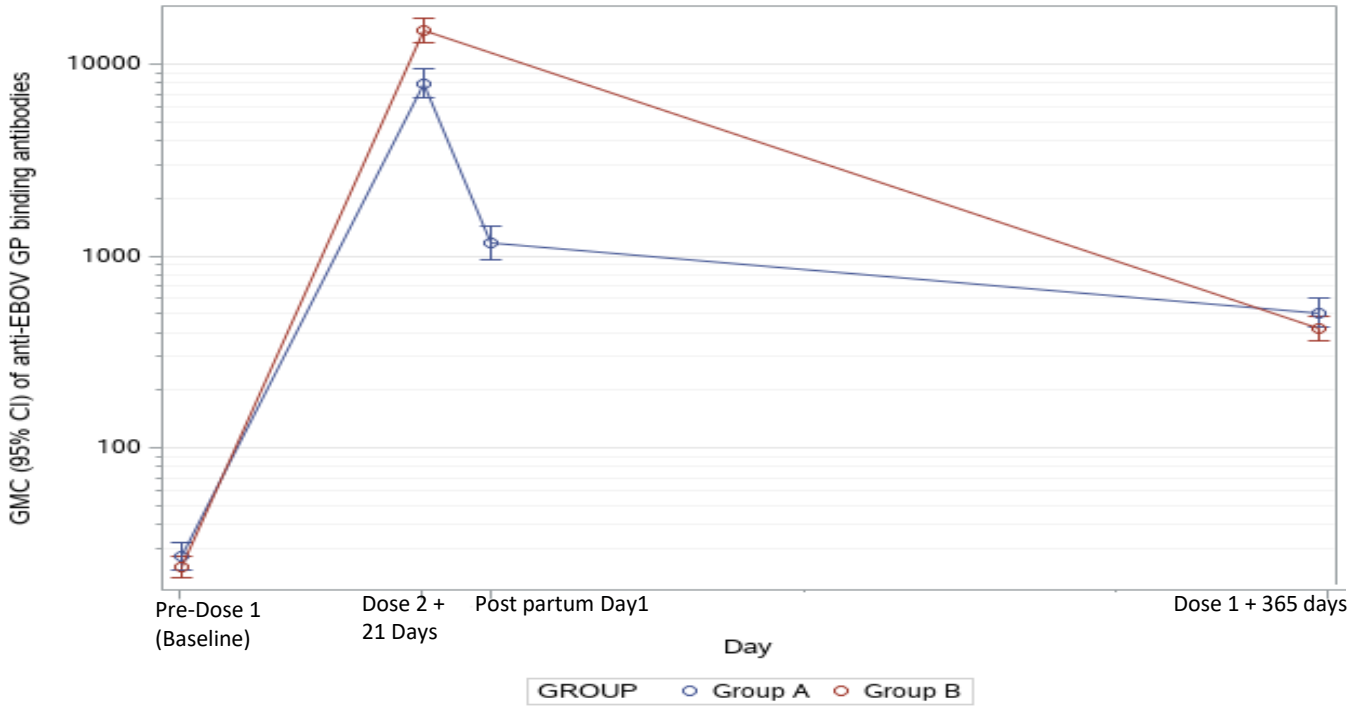
Summary of Serious Adverse Events (SAEs), with three most frequent SAEs

	Group A	Group B
N	964	981
Participants with 1 or more SAEs	211 (21.9%)	156 (15.9%)
Hospitalization	73 (7.6%)	71 (7.2%)
Neonatal infection	52 (5.4%)	30 (3.1%)
Premature baby	26 (2.7%)	30 (3.1%)

The percentage of infants with **1 or more SAEs** is **higher** for Group A total compared to Group B total (21.9% versus 15.9%).

Immunogenicity

Anti-EBOV GP Binding Antibody Response (ELISA (ELISA Units/mL): Geometric Mean (95% CI) Profiles – Women



Anti-EBOV GP Binding Antibody Response (ELISA (ELISA Units/mL): Cord Blood

	Group A
Postpartum day 1, N	146
Geometric mean (95% CI)	2186 (1769; 2703)
Positive sample n (%) (95% CI)	145 (99.3%) (96.2; 100.0)

- For Group A women with cord blood samples, percentage of anti-EBOV GP binding antibody positivity is **99% (95% CI: 96%-100%).**

Anti-EBOV GP Binding Antibody Response (ELISA (ELISA Units/mL): Infants

	Group A
Analysis set: Per Protocol Immunogenicity Set	75
Postpartum day 99, N	75
Geometric mean (95% CI)	264 (206; 339)
Positive sample n (%) (95% CI)	71 (94.7%) (86.9; 98.5)

- For Group A infants (mothers vaccinated during pregnancy), percentage of anti-EBOV GP binding antibody positivity is **94.7% (95% CI: 86.9-98.5) at 14 weeks of age.**

Summary

- **Overall, the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen is well tolerated, and was safe with no major issues observed. The percentages of adverse maternal/fetal outcomes and adverse neonatal/infant outcomes were comparable between Group A and Group B.**

- **The percentages of participants with at least one SAE are comparable between Group A and Group B women.**

- **There were four Group A women with SAEs considered to be related to the study vaccination and one Group B woman with an AE with fatal outcome.**

- **The reactogenicity profile in Group A women is consistent with that of the previous Ebola vaccine studies, with a higher reactogenicity rates following Ad26.ZEBOV compared to MVA-BN-Filo.**

- **≥99% responder rate (>2.5-fold increase over baseline) was observed for women from both groups at 21 days post-dose 2, with magnitude of anti-EBOV GP-specific binding antibody response higher in Group B (women vaccinated post-partum) vs Group A (women vaccinated during pregnancy)**

- **Binding antibodies persist to at least 1 year post-dose 1 for women from both groups, with responder rates ≥90%.**

- **Binding antibodies detected in >99% of cord blood samples.**

- **Strong correlation observed between anti-EBOV GP-specific binding antibody responses for mothers (postpartum day 1) and cord blood (postpartum day 1)**

- Additonal data: