SYNOPSIS

Study Title: A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 2b Efficacy Study of a Heterologous Prime/Boost Vaccine Regimen of Ad26.Mos4.HIV and Aluminum Phosphate-adjuvanted Clade C gp140 in Preventing HIV-1 infection in Women in Sub-Saharan Africa

Study Number: HVTN 705 / VAC89220HPX2008

Study Phase: Phase 2b

Name of Study Vaccine: JNJ-55471468, JNJ-55471494, JNJ-55471520, JNJ-64219324, JNJ-55471585 (Ad26.Mos4.HIV, Clade C gp140), or placebo.

Name of Sponsor/Company: Janssen Vaccines & Prevention B.V.*

* 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.

The study was a collaborative effort between Janssen Vaccines & Prevention B.V. and the HIV Vaccine Trials Network (HVTN). HVTN was responsible for the operational execution of the study (including protocol writing, data management, and statistics), as well as involved in other scientific and study-related activities. As the sponsor and a cofunder of the study, Janssen Vaccines & Prevention B.V. was responsible for the oversight of the study and was involved in all study-related activities. Note that CSR writing was performed by Janssen Vaccines & Prevention B.V.

Status: Approved

Date: 13 May 2024

Prepared by: Janssen Vaccines & Prevention B.V.

Study Name: Imbokodo

Clinical Registry Number: CR108263

Regulatory Agency Identifier Number: NCT03060629

Number of Study Center(s) and Countries/Territories: This study was conducted at 23 sites that enrolled participants in 5 countries in sub-Saharan Africa (ie, Malawi, Mozambique, Republic of South Africa, Zambia, and Zimbabwe).

Publications (if any): None

Study Period: 3 November 2017 (date first participant was screened) to 2 February 2022 (date of last participant last visit).

Rationale:

The present study, a Phase 2b proof-of-concept efficacy study, was conducted to evaluate the preventive vaccine efficacy (VE), safety, and tolerability of a heterologous regimen with 4 vaccinations consisting of tetravalent Ad26.Mos4.HIV and aluminum phosphate-adjuvanted Clade C gp140 in human immunodeficiency virus (HIV)-uninfected sexually active women aged 18 to 35 years.

A heterologous regimen was used, consisting of Ad26.Mos4.HIV (Vaccinations 1 and 2 at Months 0 and 3, respectively) followed by the coadministration of Ad26.Mos4.HIV with aluminum phosphate-adjuvanted Clade C gp140 (Vaccinations 3 and 4 at Months 6 and 12, respectively). The immune response was expected to be active across clades, because animal studies had shown cross clade immunogenicity.

The study enrolled female participants from populations at high risk of acquiring HIV-1 infection in settings in sub-Saharan Africa with overall moderate to high HIV-1 incidence, predominantly with Clade C. Women in these settings have among the highest HIV-1 infection rates globally, making them one of the populations in greatest need of effective prevention interventions.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the preventive VE of a heterologous regimen utilizing Ad26.Mos4.HIV and aluminum phosphate-adjuvanted Clade C gp140 for the prevention of HIV-1 infection in HIV-seronegative women residing in sub-Saharan Africa from confirmed HIV-1 infections diagnosed between the Month 7 and Month 24 visits.	• VE as derived from confirmed HIV-1 infections diagnosed between the Month 7 and Month 24 visits.
• To evaluate the safety and tolerability of a heterologous regimen utilizing Ad26.Mos4.HIV and aluminum phosphate-adjuvanted Clade C gp140 for the prevention of HIV-1 infection in HIV-seronegative women residing in sub-Saharan Africa.	• Local and systemic reactogenicity signs and symptoms for 3 days after each vaccination, adverse events (AEs) for 30 days after each vaccination, and serious adverse events (SAEs), adverse events of special interest (AESIs), and AEs leading to early participant withdrawal or early discontinuation of study product(s) administration for the entire duration of the study.
Secondary	
• To evaluate VE from enrollment through 24 months.	• HIV-1 infection diagnosed after enrollment through 24 months post enrollment.
• To evaluate VE from enrollment through the end of the study if Stage 2 occurs. [#]	• HIV-1 infection diagnosed after enrollment through the end of the study.
• To evaluate VE from Month 12 through Month 24.	• HIV-1 infection diagnosed after Month 12 through 24 months post enrollment.
• To evaluate VE from Month 12 through the end of the study if Stage 2 occurs. [#]	• HIV-1 infection diagnosed after Month 12 through the end of the study post enrollment.
• To evaluate the immunogenicity of the vaccine regimen.	• Immune responses at the study visits following the third and fourth vaccinations from assays based on the HVTN Laboratory Assay Algorithm such as vaccine-specific binding antibodies and T-cell responses.

• To evaluate immunogenicity and immune response biomarkers among vaccine recipients after the third vaccination as correlates of risk of subsequent HIV-1 acquisition and correlates of VE, if deemed applicable.	• Immune responses from assays based on the HVTN Laboratory Assay Algorithm (available at https://atlas.scharp.org/) and/or more assays down-selected from a larger pool of pilot studies, in HIV-1-infected vaccine cases and HIV-1-uninfected vaccine controls.
• To evaluate VE adjusting for various demographic and other baseline characteristics.	• HIV-1 infection diagnosed after the third vaccination by demographic and other baseline characteristics.
• If significant positive evidence of VE from Month 7 through 24 months is seen, to assess if and how VE depends on genotypic characteristics of HIV-1 such as signature mutations. [#]	• HIV-1 infection diagnosed after Month 7 through Month 24 and genotypic characteristics of viral sequences from HIV-1-infected participants at HIV-1 diagnosis, such as signature site mutations.
• To evaluate and compare genomic sequences of viral isolates from HIV-1-infected vaccine and placebo recipients, and use sieve analysis methods to assess whether VE differs by genotypic or phenotypic characteristics of exposing HIV-1s and whether there is evidence of vaccine-induced immune pressure on the viral sequences.	• Viral sequences from HIV-1-infected participants at the earliest available postinfection timepoint and possible subsequent visits.
[#] Per protocol, the secondary objectives indicated with an "#" were only to be assessed if Stage 2 occurred (ie, if significant positive evidence of VE from Month 7 through 24 months was seen). These objectives were assessed although the aforementioned conditions were not met.	

Statistical Analyses:

Sample Size Determination: The sample size calculations were based on the power of a 1-sided 0.025-level Wald test for comparing cumulative incidences of HIV-1 infection diagnosed between the Month 7 and Month 24 visits between randomized groups, in the presence of the sequential monitoring. The study was designed so that a 0.025-level Wald test has approximately 90% power in the Per-Protocol (PP) population to reject the H0 for the primary efficacy endpoint, ie, H0: VE(7-24) ≤0%. A total of 2,600 HIV-uninfected adult women provided enough power for assessing the primary efficacy endpoint and provided enough participants for safety assessment.

Analysis Sets:

- Full Analysis Set (FAS): all randomized participants who received at least 1 study vaccine administration.
- Modified Intent-to-Treat (MITT) Population: participants in the FAS who were HIV-1 uninfected on the date of first vaccination.
- Per-Protocol (PP) Population: participants in the FAS who were HIV-1 uninfected 4 weeks after the third vaccination visit, who received all planned vaccinations at the first 3 vaccination visits within the

respective visit windows, and had no other major protocol deviations that were judged to possibly impact the efficacy of the vaccine.

- Full Immunization Set (FIS): participants in the FAS who were HIV-1 uninfected 4 weeks after the fourth vaccination visit and who received all planned vaccinations within the respective visit windows.

Efficacy:

The analysis of the primary efficacy endpoint was based on the PP population. The ratio of cumulative incidences of HIV-1 infection between Months 7 and 24 (vaccine versus placebo) was estimated using the transformed Nelson-Aalen cumulative hazard function estimator and tested via a Wald test. A Cox proportional hazards model was used for estimating VE(7-24), measured by 1 minus the hazard ratio (vaccine versus placebo) and for score testing whether the VE(7-24) differed from 0%. As a sensitivity analysis, targeted minimum loss-based estimation was used to estimate the cumulative incidences of HIV-1 infection over time for each of the vaccine and placebo groups, through to the final timepoint Month 24. This analysis could correct for bias due to measured participant covariates that predict both per-protocol status and HIV-1 infection. In addition, to assess potential time-effects of VE, the Kaplan-Meier method was used to plot the estimated cumulative incidence rates over time for the vaccine and placebo groups.

Secondary analyses of VE were based on the MITT population, the PP population, and the FIS:

- VE for MITT: The analysis to evaluate the primary efficacy endpoint was repeated for the MITT population.
- VE over time periods other than between Months 7 and 24: The analysis to evaluate the primary efficacy endpoint was repeated for windows other than between Months 7 and 24 for the MITT population, PP population, and FIS.
- VE estimates between Months 7 and 24 adjusting for demographic and other baseline covariates via supervised learning for the PP population.

Note: Upon implementation of the final analysis, it became clear that the SAP version used for the primary analysis of VE did not specify an adequate statistical analysis of the primary parameter of per-protocol VE through 24 months. The statistical method that was used for the interim Data Safety Monitoring Board (DSMB) VE estimation should not have been carried over to the primary analysis of the VE. The method used for the interim DSMB analysis, when applied for the primary analysis, censored HIV-uninfected participants at the actual time of their last negative HIV sample, whereby, the VE was estimated based on the cumulative incidence rate at the moment when at least 150 participants were still in the risk set in each group of the PP population. As such more than 80% of the participants were censored because their actual visit time was before the moment in the study when there were still 150 participants per group in the PP population. The SAP was updated to correct this. This ascertainment was based purely on methodological grounds and was not influenced by the results. For additional details refer to the SAP. In this CSR, only the correct VE estimates are reported.

Safety: The analyses of safety were performed on the FAS and tabulated by study vaccine group (ie, actual study vaccine received, vaccine or placebo). The safety analysis included descriptive summaries of AEs: solicited local and systemic AEs, unsolicited AEs, SAEs, AESIs, and AEs leading to discontinuation from study vaccine or early study termination. Solicited AEs were summarized by maximum severity and by 3- or 7-day FU. Solicited systemic AEs were also summarized by relationship to study vaccine. Unsolicited AEs and SAEs were summarized by SOC, PT, maximum severity, and relationship to study vaccine. Kruskal-Wallis tests were used to test for differences in severity of solicited AEs between the vaccine and placebo groups. No other formal statistical testing was planned.

Immunogenicity: Data from quantitative assays were summarized (tabulated/graphically presented per timepoint available) by study vaccine group: N, geometric means and corresponding 95% CIs, and percentage positive responses/responders (if available).

Methodology:

This was a randomized, double-blind, placebo-controlled, parallel-group, Phase 2b proof-of-concept efficacy study conducted at multiple sites in sub-Saharan Africa that evaluated the preventive VE, safety, and tolerability of a heterologous regimen with 4 vaccinations (at Months 0, 3, 6, and 12) consisting of tetravalent Ad26.Mos4.HIV and aluminum phosphate-adjuvanted Clade C gp140 in HIV-uninfected sexually active female participants aged 18 to 35 years. Participants were to be selected from populations at high risk of acquiring HIV-1 infection with overall moderate to high HIV-1 incidence, predominantly Clade C. The planned total sample size was approximately 2,600 participants randomized in a 1:1 ratio to the vaccine or placebo group. All study vaccines were administered intramuscularly (IM).

A schematic overview of the study vaccination schedule is presented in the table below.

		Month 0	Month 3	Month 6	Month 12
Group	**N**	**Vaccination 1**	**Vaccination 2**	**Vaccination 3**	**Vaccination 4**
1	1,300	Ad26.Mos4.HIV[a]	Ad26.Mos4.HIV[a]	Ad26.Mos4.HIV[a] + Clade C gp140[b]	Ad26.Mos4.HIV[a] + Clade C gp140[b]
2	1,300	Placebo[c]	Placebo[c]	Placebo[c] + Placebo[c]	Placebo[c] + Placebo[c]

[a] 5×10^{10} vp Ad26.Mos4.HIV per 0.5 mL IM injection.
[b] 250 mcg Clade C gp140 glycoprotein (corresponding with 80 mcg Clade C gp140 protein) and 425 mcg (Al content) aluminum phosphate adjuvant per 0.5 mL IM injection.
[c] Sterile 0.9% saline, 0.5 mL IM injection. Same type of placebo used at all timepoints.

The study design consisted of 2 stages. Stage 1 was defined as the calendar time since the study start until the last enrolled participant reached the Month 24 visit. Stage 2 was defined as the calendar time since the last enrolled participant reached the Month 24 visit until the last enrolled participant reached the Month 36 visit. Participants were followed for HIV-1 infection (every 3 months) for a period of at least 2 years after enrollment until the primary analysis at the end of Stage 1 (when the last participant reached the Month 24 visit) was performed. Pending availability and outcome of primary analysis results, participants continued their normal scheduled visits beyond Month 24. If the primary efficacy endpoint was not met, then the study was not to proceed to Stage 2 as defined per protocol and all participants were to be unblinded at the end of Stage 1.

Safety was monitored on ongoing basis by study responsible physicians, and routinely by the Protocol Safety Review Team (PSRT). In addition, an independent DSMB periodically reviewed study data, including unblinded study data if needed. The Oversight Group, with senior representatives from the sponsor and other cofunders, provided the overall scientific direction for the study, and received and decided on any recommendations made by the DSMB.

The pre-specified criteria to continue with Stage 2 of the study (until Month 36) were not met (primary efficacy endpoint not met, see below).

Number of Participants (planned and analyzed):

Participant Disposition; All Participants Analysis Set (VAC89220HPX2008)

	Total	Placebo	Vaccine
Planned	2,600	1,300	1,300
Randomized	2,654	1,328	1,326
Enrolled (received at least 1 dose of study vaccine)	2,636	1,323	1,313
FAS (assigned study vaccine)	2,636	1,323	1,313
FAS (actual study vaccine)	2,636	1,319	1,317
MITT	2,630	1,319	1,311
PP	2,188	1,108	1,080
FIS	1,976	995	981

Diagnosis and Main Criteria for Inclusion and Exclusion:

The study population consisted of healthy, HIV-uninfected, sexually active women (assigned female sex at birth) aged 18 to 35 years, who were considered to be at risk for HIV-1 infection by the site staff.

Study Vaccines, Dose, and Mode of Administration:

- Group 1:
  - Ad26.Mos4.HIV 5×10^{10} vp to be administered as 0.5 mL IM into the left deltoid (unless medically contraindicated) on Months 0, 3, 6, and 12.
  - Clade C gp140 (250 mcg) mixed with Aluminum phosphate adjuvant to be administered as 0.5 mL IM into the right deltoid (unless medically contraindicated) on Months 6 and 12.
- Group 2:
  - Placebo for Ad26.Mos4.HIV (ie, sodium chloride for injection USP, 0.9%) to be administered as 0.5 mL IM into the left deltoid (unless medically contraindicated) on Months 0, 3, 6, and 12.
  - Placebo for Clade C gp140 / Aluminum phosphate adjuvant (ie, sodium chloride for injection USP, 0.9%) to be administered as 0.5 mL IM into the right deltoid (unless medically contraindicated) on Months 6 and 12.

Duration of Study Vaccination:

A 12-month study vaccination schedule, where participants were vaccinated at Months 0, 3, 6, and 12.

SUMMARY OF RESULTS AND CONCLUSIONS:

Study Disposition:

Of the 5,221 participants screened for the study, 2,654 participants were randomized. Of the randomized participants, 2,636 (99.3%) were enrolled and received at least 1 dose of study vaccine (vaccine: 1,313 [99.0%] and placebo: 1,323 [99.6%]). Of these, 2,441 (92.6%) participants completed all study vaccinations (vaccine: 1,213 [92.4%] and placebo: 1,228 [92.8%]). The majority of participants terminated the study early because the study was terminated by the sponsor after Stage 1 (ie, when the last enrolled participant completed the Month 24 visit) as the pre-specified criteria to continue with Stage 2 of the study (until Month 36) were not met, ie, 2,223 (84.3%) participants. However, FU data after the Month 24 visit are available, as the majority of the participants already passed the Month 30 visit at the time of the primary analysis.

Protocol Deviations:

Overall, major protocol deviations were reported for 357 (13.5%) participants. For 5 (0.2%) participants, a major protocol deviation affecting efficacy was reported: 4 in the vaccine group (ie, 3 study vaccine administration errors and 1 inappropriate enrollment) and 1 in the placebo group (ie, conduct of non-protocol procedure). These 5 participants were excluded from the PP population.

Demographic and Other Baseline Characteristics:

The demographic characteristics were comparable between the vaccine and placebo groups. The median age was 23 years (range 18 to 35 years), and the median body mass index was 25 kg/m² (range 15 to 60 kg/m²). The majority of participants were black (99.4%).

The self-reported risk behaviors and STI testing results at baseline were comparable between the vaccine and placebo groups. At baseline, participants reported a median of 2 sex partners in the last month, 88.5% of participants reported to never or only sometimes use a condom, 45.6% of participants reported to exchange sex for money/gifts, and 32.0% of participants had a positive STI test result (for any of the tested STIs).

Exposure:

All enrolled participants received at least 1 vaccination, ie, Vaccination 1. Adherence to study vaccinations was comparable between the vaccine and placebo groups at all vaccination timepoints.

Efficacy Results:

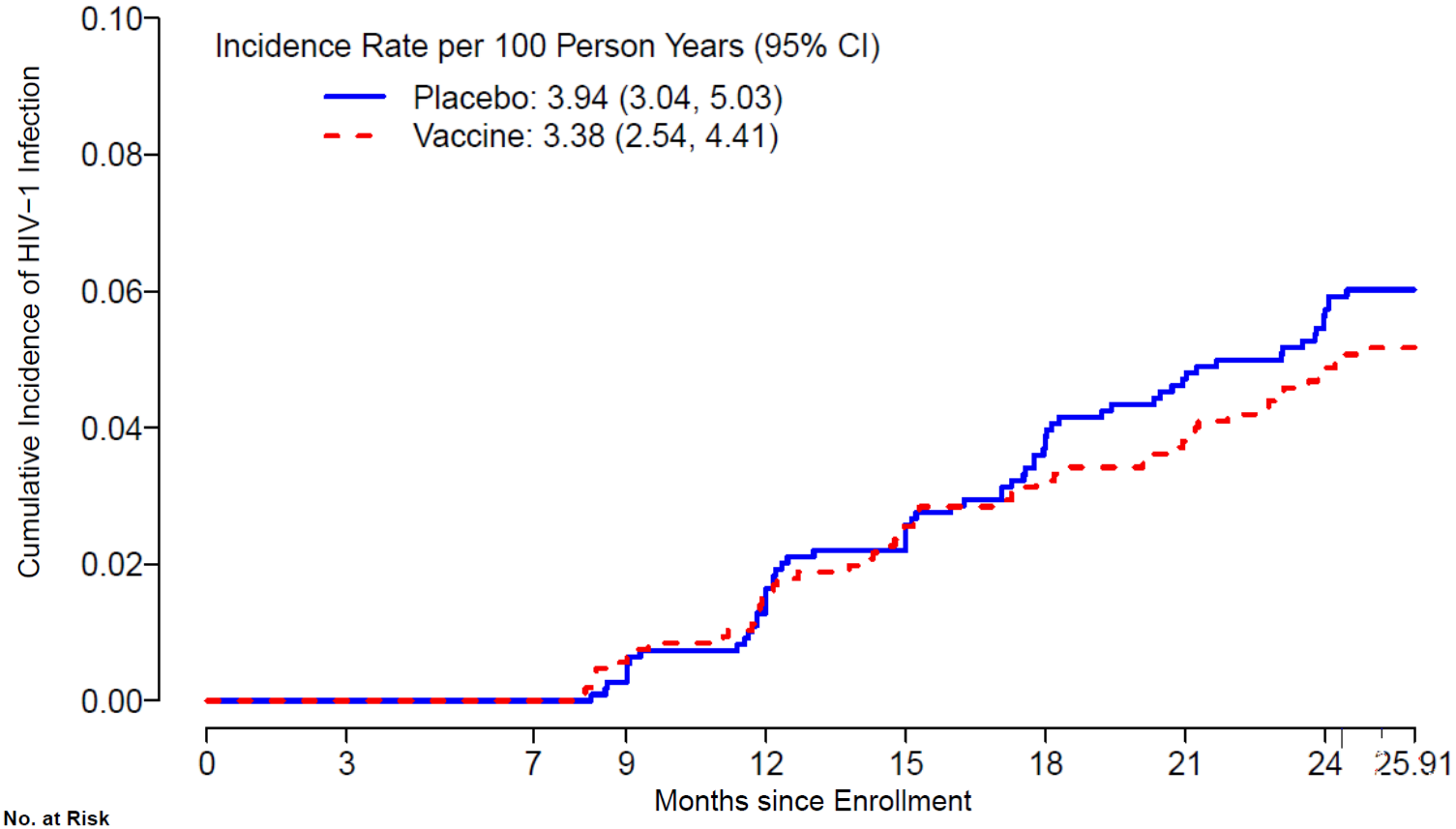
- Point estimates of VE for the primary and secondary efficacy endpoints are presented in the table below.

Point Estimates of VE for the Primary and Secondary Efficacy Endpoints (VAC89220HPX2008)

Endpoint (Time Period in Months)	Analysis set	Cumulative Incidence Ratio-based VE Point Estimate (%) (95% CI) *(2-sided p-value)*
Primary Efficacy Endpoint		
VE(7-24)	PP	14.10% (-22.00% to 39.51%) *(p=0.40)*
Secondary Efficacy Endpoints		
VE(7-24)	MITT	7.01% (-30.31% to 33.65%) *(p=0.67)*
VE(0-24)	MITT	8.78% (-19.68% to 30.48%) *(p=0.51)*
VE(13-24)	MITT	-4.65% (-64.38% to 33.37%) *(p=0.84)*
VE(13-24)	FIS	6.82% (-49.26% to 41.83%) *(p=0.77)*

- The protocol-defined primary efficacy endpoint was not met, as the VE to prevent HIV-1 infection between Months 7 and 24 in the PP population did not differ significantly from zero. Point estimates for the cumulative HIV-1 incidence (per 100 person-years) in the vaccine and placebo groups were similar between Months 7 and 15, and were higher in the placebo group between Months 15 and 18 and this difference was stable afterwards (see figure on next page).
- Secondary analyses of VE (between Months 7 and 24, Months 0 and 24, and Months 13 and 24 in the MITT population and between Months 13 and 24 in the FIS) and additional analyses of VE (for additional timepoints including through Month 36 for the MITT population, PP population, and FIS) also showed that VE did not differ significantly from zero.
- The cumulative incidence ratio-based VE point estimate (95% CI) by adjusting for demographic and other baseline covariates (13.64% [-23.19% to 39.45%]) was similar to the unadjusted estimate reported for the primary efficacy endpoint. These results suggest that baseline covariates are at most weakly predictive of the HIV-1 endpoint and loss to FU time, and support that the independent censoring assumption needed for the primary endpoint analysis was a valid assumption.

Cumulative HIV-1 Incidence Over 7 to 24 Months; PP Population (VAC89220HPX2008)



No. at Risk										
Placebo	1108	1108	1099	1091	1071	1052	1034	1019	1008	1004
Vaccine	1080	1080	1067	1056	1039	1019	1002	991	975	972
Cumulative HIV−1 Infections										
Placebo	0	0	0	3	18	28	42	51	62	65
Vaccine	0	0	0	6	17	27	34	40	51	54

Censored at $\tau = 25.91$ months.

Safety Results:

Solicited Local and Systemic Adverse Events

- Solicited AEs were followed and collected for 3 or 7 days after each vaccination depending on the study site. Out of the 23 sites, 20 sites followed and collected solicited AEs for 3 days after each vaccination and 3 sites for 7 days after each vaccination.
- A summary of all solicited local and systemic AEs, followed and collected for 3 or 7 days after each vaccination depending on the study site, is provided in the table on the next page (after any vaccination).

Solicited Local Adverse Events:

- After any vaccination, 37.2% of participants reported solicited local AEs (followed and collected for 3 or 7 days). The frequency of participants with solicited local AEs was higher in the vaccine group (51.1%) compared with the placebo group (23.4%). More participants in the vaccine group reported solicited local AEs after Vaccination 1 (34.2%) versus after Vaccination 2 (20.0%), after Vaccination 3 (25.2%), and after Vaccination 4 (25.7%). This trend was not observed for the placebo group (frequency ranged from 8.1% to 9.4% after Vaccinations 1, 2, 3, and 4).
- After any vaccination, the most frequent solicited local AE was pain/tenderness (50.3% in the vaccine group versus 23.0% in the placebo group).
- Most solicited local AEs were of Grade 1 or 2 in severity. Solicited local AEs of Grade 3 were reported in 10 (0.8%) and 3 (0.2%) participants for the vaccine and placebo group, respectively. No solicited local AEs of Grade 4 were reported.
- All solicited local AEs were transient in nature and presumed related to study vaccine by definition.

Solicited Systemic Adverse Events:

- After any vaccination, 63.7% of participants reported solicited systemic AEs (followed and collected for 3 or 7 days). The frequency of participants with solicited systemic AEs was higher in the vaccine group (68.1%) compared with the placebo group (59.4%), but this was less pronounced than for the solicited local AEs. More participants reported solicited systemic AEs after Vaccination 1 (52.9% and 40.9% in the vaccine and placebo group, respectively) versus after Vaccination 2 (33.2% and 28.6%), after Vaccination 3 (31.5% and 26.8%), and after Vaccination 4 (29.4% and 23.6%).
- The frequency of participants with solicited systemic AEs was higher in the vaccine group (66.8%) compared with the placebo group (56.3%) when solicited systemic AEs were followed and collected for 3 days after each vaccination, whereas this was comparable between both groups (73.9% and 73.3%, respectively) when solicited systemics AEs were followed and collected for 7 days after each vaccination.
- After any vaccination, the most frequent solicited systemic AEs were headache (56.9% and 46.2% in the vaccine and placebo group, respectively) and malaise and/or fatigue (48.4% and 35.3%).
- After any vaccination, most solicited systemic AEs were of Grade 1 or 2 in severity. Solicited systemic AEs of Grade 3 were reported in 32 (2.4%) and 19 (1.4%) participants for the vaccine and placebo group, respectively. Solicited systemic AEs of Grade 4 were reported in 2 (0.2%) and 1 (0.1%) participant(s) for the vaccine and placebo group, respectively, all involving pyrexia (temperature ≥40.0°C).
- All reported solicited systemic AEs were transient in nature.

Summary Table of Solicited AEs; After Any Vaccination; Full Analysis Set (VAC89220HPX2008)

	Combined FU						3-day FU				7-day FU*			
Participants With 1 or More AEs (%)	Total (N=2,636)		Placebo (N=1,319)		Vaccine (N=1,317)		Placebo (N=1,079)		Vaccine (N=1,076)		Placebo (N=240)		Vaccine (N=241)	
After Any Vaccination														
Solicited AE	1,773	(67.3%)	814	(61.7%)	959	(72.8%)	635	(58.9%)	771	(71.7%)	179	(74.6%)	188	(78.0%)
Solicited AE of Grade 3 or 4	62	(2.4%)	22	(1.7%)	40	(3.0%)	16	(1.5%)	32	(3.0%)	6	(2.5%)	8	(3.3%)
Solicited local AE	981	(37.2%)	308	(23.4%)	673	(51.1%)	237	(22.0%)	528	(49.1%)	71	(29.6%)	145	(60.2%)
Solicited local AE of Grade 3 or 4	13	(0.5%)	3	(0.2%)	10	(0.8%)	3	(0.3%)	7	(0.7%)	0	(0.0%)	3	(1.2%)
Solicited systemic AE	1,680	(63.7%)	783	(59.4%)	897	(68.1%)	607	(56.3%)	719	(66.8%)	176	(73.3%)	178	(73.9%)
Solicited systemic AE of Grade 3 or 4	54	(2.0%)	20	(1.5%)	34	(2.6%)	14	(1.3%)	28	(2.6%)	6	(2.5%)	6	(2.5%)
Solicited systemic AE that is thought to be related to study vaccine**	1,341	(50.9%)	610	(46.2%)	731	(55.5%)	455	(42.2%)	563	(52.3%)	155	(64.6%)	168	(69.7%)
Solicited systemic AE of Grade 3 or 4 and that is thought to be related to study vaccine**	26	(1.0%)	11	(0.8%)	15	(1.1%)	8	(0.7%)	14	(1.3%)	3	(1.3%)	1	(0.4%)

* Participants for which 7-day solicited AEs were collected are only shown in the respective columns (7-day FU). Their reactogenicity in the first 3 days is not reflected in the columns showing the 3-day reactogenicity data.
** Excluding temperature, as relationship to study vaccine for “temperature” was not collected.
Participants were counted once per solicited AE according to the maximum severity level experienced across all vaccinations.
Percentages were calculated as the count divided by the number of participants receiving a specified study vaccine x100.

Solicited Systemic Adverse Events Considered Related to Study Vaccine by the Investigator:

- Solicited systemic AEs were assigned an attribution by the investigator, except for temperature, as relationship to study vaccine for temperature was not collected.
- The majority of solicited systemic AEs (excluding temperature) were considered related to study vaccine by the investigator. After any vaccination, 55.5% and 46.2% of participants reported solicited systemic AEs considered related to study vaccine in the vaccine and placebo group, respectively. More participants reported solicited systemic AEs considered related to study vaccine after Vaccination 1 (41.0% and 30.8% in the vaccine and placebo group, respectively) versus after Vaccination 2 (25.0% and 21.4%), after Vaccination 3 (24.4% and 19.3%), and after Vaccination 4 (24.5% and 17.2%).
- After any vaccination, the most frequent related solicited systemic AEs were malaise and/or fatigue (21.3% and 17.0% in the vaccine and placebo group, respectively) and headache (12.3% and 13.8%).
- After any vaccination, most related solicited systemic AEs were of Grade 1 or 2 in severity. Related solicited systemic AEs of Grade 3 were reported for 15 (1.1%) and 11 (0.8%) participants in the vaccine and placebo group, respectively. These Grade 3 AEs included malaise and/or fatigue, arthralgia, chills, headache, and myalgia. No related solicited systemic AEs of Grade 4 were reported.

Unsolicited Adverse Events

- A summary of unsolicited AEs reported within 30 days after each vaccination is provided in the table below (after any vaccination)

Summary Table of Unsolicited AEs, Discontinuations Due to AEs, AESIs, and SAEs; After Any Vaccination; Full Analysis Set (VAC89220HPX2008)

Participants With 1 or More AEs (%)	Total (N=2,636)		Placebo (N=1,319)		Vaccine (N=1,317)	
After Any Vaccination						
Unsolicited AE	1,941	(73.6%)	961	(72.9%)	980	(74.4%)
Unsolicited AE with severity Grade 1 as worst grade	87	(3.3%)	46	(3.5%)	41	(3.1%)
Unsolicited AE with severity Grade 2 as worst grade	1,751	(66.4%)	869	(65.9%)	882	(67.0%)
Unsolicited AE with severity Grade 3 as worst grade	83	(3.1%)	39	(3.0%)	44	(3.3%)
Unsolicited AE with severity Grade 4 as worst grade	10	(0.4%)	3	(0.2%)	7	(0.5%)
Unsolicited AE that is thought to be related to study vaccine	23	(0.9%)	11	(0.8%)	12	(0.9%)
Unsolicited AE with worst severity Grade 3 or 4 and that is thought to be related to study vaccine	1	(0.0%)	1	(0.1%)	0	(0.0%)
AE leading to permanent stop of study vaccine[a]	6	(0.2%)	3	(0.2%)	3	(0.2%)
AE of special interest	5	(0.2%)	3	(0.2%)	2	(0.2%)
SAE	86	(3.3%)	37	(2.8%)	49	(3.7%)
SAE that is thought to be related to study vaccine	0	(0.0%)	0	(0.0%)	0	(0.0%)
SAE with fatal outcome[b]	10	(0.4%)	4	(0.3%)	6	(0.5%)

[a] One of the unsolicited AEs leading to discontinuation from study vaccine in the vaccine group was a fatal AE.
[b] One fatal AE occurred in the offspring of a participant in the vaccine group.
Participants may appear in more than one category.
Participants were counted once per unsolicited AE according to the maximum severity level experienced across all vaccinations.
Percentages were calculated as the count divided by the number of participants receiving a specified study vaccine x100.

- After any vaccination, 73.6% of participants reported unsolicited AEs; the frequency was comparable between the vaccine (74.4%) and the placebo group (72.9%). Most unsolicited AEs were reported after Vaccination 4 (63.5% and 62.5% in the vaccine and placebo group, respectively), followed by after Vaccination 3 (39.8% and 40.3%), and after Vaccination 2 (17.1% and 15.1%) and Vaccination 1 (16.6% and 14.8%). This observation is most likely due to the high contribution of STIs, which were collected and reported throughout the study, in combination with the longer duration of the after Vaccination 4 periods (at least 6 months) and after Vaccination 3 periods (6 months) compared with the after Vaccination 2 and 1 periods (3 months each).
- After any vaccination, the most frequently involved SOC was infections and infestations (63.6% and 63.3% in the vaccine and placebo group, respectively). The most frequently reported unsolicited AEs were STIs, with as most common per PTs: genitourinary chlamydia infection (40.1% and 40.0% in the vaccine and placebo group, respectively), genitourinary tract gonococcal infection (20.4% and 21.8%), and vulvovaginitis trichomonal (18.6% and 18.1%). The high frequency of STIs observed during the study was to be expected because the study enrolled sexually active women who were considered to be at risk for HIV-1 infection by the site staff, 88.5% of participants reported to never or only sometimes use a condom, and 32.0% of participants had a positive STI test result at baseline (for any of the tested STIs).
- After any vaccination, the majority of unsolicited AEs were Grade 2 in severity. Fewer than 3.5% of participants in either group experienced unsolicited AEs of Grade 3 (3.3% and 3.0% in the vaccine and placebo group, respectively). Grade 4 unsolicited AEs were reported in 7 (0.5%) and 3 (0.2%) participants in the vaccine and placebo group, respectively. Grade 5 (fatal) unsolicited AEs are discussed below.

Unsolicited Adverse Events Considered Related to Study Vaccine by the Investigator:

- Few unsolicited AEs were considered related to study vaccine by the investigator. After any vaccination, 12 (0.9%) and 11 (0.8%) participants reported unsolicited AEs considered related to study vaccine in the vaccine and placebo group, respectively. The frequency of participants with unsolicited AEs considered related to study vaccine was generally similar with each successive vaccination and ranged from 0.1% to 0.5%.
- After any vaccination, the most frequent related unsolicited AEs by PT were dizziness (3 participants in the vaccine group and 2 in the placebo group), injection site pruritus (3 participants in the vaccine group and 1 in the placebo group), pruritis (2 participants in both the vaccine and placebo groups), and urticaria (2 participants in the placebo group). The other related unsolicited AEs occurred in at most 1 participant.
- After any vaccination, most related unsolicited AEs were of Grade 1 or 2 in severity. Related unsolicited AEs of Grade 2 were reported in 3 participants of the vaccine group (pruritus, headache, and injection site cellulitis by PT) and 4 in the placebo group (pruritus, rash, macular rash, and eye pain by PT). One participant in the placebo group experienced 2 Grade 3 AEs that were considered related to study vaccine (urticaria and hypersensitivity by PT). No related unsolicited AEs of Grade 4 or Grade 5 (fatal AEs) were reported.

Deaths, Serious Adverse Events, Discontinuations due to Adverse Events, Adverse Events of Special Interest, and Other Significant Adverse Events

- Nine participants experienced a Grade 5 (fatal) AE: 5 (0.4%) participants in the vaccine group (ie, stab wound, headache, abdominal mass, alcoholic psychosis, anaemia, and respiratory tract infection; anaemia and respiratory tract infection occurred in the same participant) and 4 (0.3%) participants in the placebo group (ie, maternal death during childbirth, death, pneumonia, and gun shot wound). Additionally, 1 Grade 5 (fatal) AE occurred in the offspring of a participant in the vaccine group. The offspring died on the day of birth and the AE was reported as congenital anomaly in offspring. None of the fatal AEs were considered related to study vaccine by the investigator.
- SAEs were reported in 49 (3.7%) participants in the vaccine group and 37 (2.8%) participants in the placebo group. Four (0.2%) participants (2 in the vaccine group and 2 in the placebo group) reported a congenital anomaly in the offspring. None of the SAEs were considered related to study vaccine by the investigator.
- Of all participants, 6 (0.2%) discontinued study vaccine due to an unsolicited AE: 3 (0.2%) participants in the vaccine group (idiopathic intracranial hypertension of Grade 3 in severity considered not related to study vaccine by the investigator and continuing at the end of study participation, stab wound of Grade 5 [fatal] in severity considered not related to study vaccine by the investigator, and pruritus of Grade 2 in severity considered related to study vaccine by the investigator and resolved after 1 day) and 3 (0.2%) in the placebo group (hypersensitivity of Grade 3 in severity resolved within 1 day, rash of Grade 2 in severity resolved within 1 day, and macular rash of Grade 2 in severity resolved within 2 days; all considered related to study vaccine by the investigator). Four (0.2%) participants discontinued study vaccine due to a solicited AE: 3 (0.2%) participants in the vaccine group (pyrexia of Grade 4 [temperature ≥40.0°C] in 2 participants [resolved after 1 day in 1 participant and after 2 days in the other participant] and erythema/redness of Grade 3 at the Ad26.Mos4.HIV injection site considered related to study vaccine by the investigator and resolved after 2 days) and 1 (0.1%) in the placebo group (pyrexia of Grade 4 [temperature ≥40.0°C] resolved after 3 days). No participants discontinued the study due to an AE.
- The list of predefined AESIs for this study included but was not limited to potential immune-mediated diseases (including neuroinflammatory disorders, musculoskeletal disorders, skin disorders, metabolic disorders, blood disorders, vasculitides, gastrointestinal disorders, liver disorders, and others). AESIs were reported in 2 (0.2%) participants in the vaccine group (moderate toxic nodular goiter and severe type 1 diabetes mellitus) and 3 (0.2%) participants in the placebo group (moderate lichen planus and 2 cases of severe type 1 diabetes mellitus). None of the AESIs were considered related to study vaccine by the investigator.
- There were no cases of concurrent thrombosis with thrombocytopenia.
- Overall, 451 pregnancies were reported during the study, of which 239 in the vaccine group and 212 in the placebo group. Pregnancy outcomes were reported for 366 pregnancies (191 and 175 in the vaccine and placebo group, respectively). Most pregnancy outcomes (260 [71.0%]) reported a full-term live birth (134 [70.2%] and 126 [72.0%] in the vaccine and placebo group, respectively). Four (0.2%) participants (2 in the vaccine group and 2 in the placebo group) reported a fetal/congenital anomaly in the offspring; which were considered SAEs (see above).
- Of the 451 pregnancies reported during the study, 61 pregnancies occurred during the prohibited period (ie, 21 days prior to enrollment through 3 months after the last vaccination); 31 and 30 pregnancies in the vaccine and placebo group, respectively. Most pregnancy outcomes (42 [68.9%]) reported a full-term live birth (18 [58.1%] and 24 [80.0%] in the vaccine and placebo group, respectively). The following abnormal outcomes were reported: 10 (16.4%) spontaneous abortions (8 [25.8%] and 2 [6.7%] in the vaccine and placebo group, respectively), 7 (11.5%) premature-term live births

(4 [12.9%] and 3 [10.0%]), and 2 (3.3%) therapeutic/elective abortions (1 in each group). No fetal/congenital anomalies were reported for these pregnancies.

Immunogenicity Results:

- Vaccine-induced binding and functional antibody responses, as well as cellular immune responses, were observed after the third vaccination, which generally increased after the fourth vaccination and waned over 1 year after completion of the vaccination series.
- IgG3 BAMA and total IgG ELISA demonstrated induction of strong gp140 binding antibodies in all participants; lower magnitudes were observed for gp120 antigens. IgG3 and total IgG antibody binding to V1V2 antigens was markedly lower and only observed in a subset of participants.
- IgA BAMA analysis demonstrated that these antibodies were induced towards the gp140 and gp120 antigens tested, but only in a very limited extent to the V1V2 antigens. Of note, IgA responses were slightly higher in cases compared to controls.
- Cellular immune responses, evaluated by ICS, showed high frequencies of antigen-specific T cells to Env peptides after the third and fourth vaccination. CD4+ T-cell responses were highest to gp120 antigens and were low to Gag or Pol antigens; CD8+ T-cell responses were comparatively lower to all Env antigens but were higher to Gag and Pol antigens.
- Case-control analysis, comparing vaccinated PP participants who had a breakthrough infection with those who remained uninfected between Months 7 and 24, did not reveal any relevant differences between cases and controls for any of the assays evaluated.
- Correlate of risk and protection analysis did not identify any immune markers significantly associated with decreased risk of HIV infection or with VE. IgG3 responses to V1V2 antigens showed a consistent trend towards being associated with decreased infection risk and increased VE across analyses, but these responses were induced in only a small proportion of the vaccine recipients and did not reach statistical significance.
- High baseline Ad26 seropositivity was reported among study participants, but this was not found to impact key immunological readouts.

Sequencing Analysis of Infecting HIV-1 Viral Isolates:

- Results of the genomic sequencing analysis of viral isolates from HIV-1-infected vaccine and placebo recipients do not support that VE depended on HIV envelope AA sequence features.

Conclusions:

- The VE to prevent HIV-1 infection between Months 7 and 24 in the PP population did not differ significantly from zero; therefore, the primary efficacy endpoint was not met.
- Secondary and additional analyses of VE (including between Months 13 and 24, and through Month 36) also did not indicate a VE that differs significantly from zero.
- The vaccine regimen evaluated in this study demonstrated acceptable safety and tolerability in HIV-uninfected women considered to be at risk for HIV-1 infection by the site staff, with no vaccine-related SAEs.
- Humoral and cellular immune responses were induced upon vaccination. Generally, responses increased from the third and fourth vaccination onwards and waned 12 months after the fourth vaccination. Correlates analysis indicated a trend for IgG3 V1V2 magnitude breadth scores to be associated with decreased infection risk, but these responses were induced in only a small proportion of the vaccine recipients and did not reach statistical significance.
- Overall, the results do not support that VE depended on HIV envelope AA sequence features.
- No notable study limitations were identified by the sponsor.

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