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Six-Month Safety Data of Recombinant Vesicular Stomatitis Virus–Zaire Ebola Virus Envelope Glycoprotein Vaccine in a Phase 3 Double-Blind, Placebo-Controlled Randomized Study in Healthy Adults

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(See the editorial commentary by Schnell on pages 1775-6.)

Background. This study (NCT02503202) evaluated the safety of recombinant vesicular stomatitis virus–Zaire Ebola virus envelope glycoprotein vaccine (rVSVΔG-ZEBOV-GP).

Methods. Overall, 1197 subjects were randomized 2:2:2:2:1; 1194 were vaccinated with 1 dose of 1 of 3 lots of rVSVΔG-ZEBOV-GP (2×10^7 plaque-forming units [pfu], n = 797; combined-lots group), a single high-dose lot of rVSVΔG-ZEBOV-GP (1×10^8 pfu, n = 264; high-dose group), or placebo (n = 133). Daily temperatures and adverse events (AEs) were recorded days 1 to 42 postvaccination. Solicited AEs included injection-site AEs from days 1 to 5, and joint pain, joint swelling, vesicular lesions (blisters), and rashes from days 1 to 42. Serious AEs (SAEs) were recorded through 6 months postvaccination.

Results. Fever (≥38.0°C) was observed in 20.2% of combined lots (3.2% with ≥39.0°C), 32.2% of high-dose (4.3% with ≥39.0°C), and 0.8% of placebo (0.8% with ≥39.0°C). Incidences of AEs of interest (days 1–42) were arthralgia (17.1% combined lots, 20.4% high-dose, 3.0% placebo), arthritis (5.1% combined lots, 4.2% high-dose, 0.0% placebo), and rash (3.8% combined lots, 3.8% high-dose, 1.5% placebo). Twenty-one SAEs and 2 deaths were reported, all assessed by investigators as unrelated to vaccine.

Conclusions. rVSVΔG-ZEBOV-GP was generally well-tolerated, with increased rates of injection-site and systemic AEs compared to placebo, and no vaccine-related SAEs or deaths. These findings support the use of rVSVΔG-ZEBOV-GP vaccine in persons at risk for Ebola virus disease.

Clinical Trials Registration. NCT02503202.

Keywords. rVSVΔG-ZEBOV-GP; Ebola; vaccine; safety.

Ebola viruses (EBOV) are members of the Filoviridae family and cause hemorrhagic fevers with high mortality [1]. Until recently, EBOV caused relatively small outbreaks in rural Central and East Africa but was associated with very high mortality rates. Prior to 2014, there were approximately 15 EBOV outbreaks reported, mostly with several to a few hundred cases [1, 2].

The recent outbreak (2014–2016) of EBOV in West Africa greatly surpassed all previous outbreaks combined in the number of cases, the number of deaths, the geographic extent, and the disruption of national healthcare systems, economies, and civil society [2]. From December 2013 until March 2015, >28 600 cases with at least 11 300 deaths (40% mortality) were reported, primarily from Liberia, Sierra Leone, and Guinea. Although several EBOV vaccines were under development prior to the West Africa outbreak, its size and scope catalyzed an international effort to accelerate development and testing of EBOV vaccines in an unprecedented manner [2].

One such EBOV vaccine uses a recombinant vesicular stomatitis virus (rVSV) as a vector to elicit an immune response against the Zaire EBOV (ZEBOV; Kikwit strain) glycoprotein (rVSVΔG-ZEBOV-GP) [3]. VSV normally infects cattle, pigs, and horses, causing mucosal lesions; humans rarely become infected and, when they do, are usually asymptomatic, although febrile influenza-like symptoms and (rarely) mucosal and skin lesions can occur [4]. In rVSVΔG-ZEBOV-GP, the gene encoding the VSV surface glycoprotein is replaced with the gene encoding the ZEBOV glycoprotein, further attenuating the virus [5]. This construct (rVSVΔG-ZEBOV-GP) has been shown to be immunogenic in rodents and in nonhuman primates and highly effective when given preexposure in nonhuman primates [5–7].

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The rVSVΔG-ZEBOV-GP vaccine was developed by the Public Health Agency of Canada and licensed initially to NewLink Genetics and subsequently to Merck & Co, Inc. A total of 8 phase 1 clinical trials were undertaken and have demonstrated rVSVΔG-ZEBOV-GP to be generally well-tolerated and immunogenic in humans [5–7]. Based on these studies, 4 large, phase 2/3 clinical trials were initiated to demonstrate safety, immunogenicity, and where possible, efficacy. This randomized, double-blind, multicenter phase 3 clinical trial (NCT02503202) was undertaken to examine the lot-to-lot consistency of rVSVΔG-ZEBOV-GP and provide further safety and immunogenicity data. The observation of a relatively high incidence of arthritis in one of the phase 1 sites prompted us to design the study in such a way that detailed information was collected about the incidence, onset, and duration of arthralgia, arthritis, and rash in a large, well-controlled study [6, 7]. We report here the preplanned, interim 6-month safety analysis.

METHODS

Design

This was a randomized, double-blind, placebo-controlled study conducted at 40 sites in the United States, 1 site in Spain, and 1 site in Canada, between 17 August 2015 and 2 May 2016. A total of 1197 healthy adults were randomized (1194 vaccinated) to receive 1 of 3 consistency lots of rVSVΔG-ZEBOV-GP vaccine (2×10^7 plaque-forming units [pfu]), a high dose of rVSVΔG-ZEBOV-GP vaccine (1×10^8 pfu), or placebo in a 2:2:2:2:1 ratio. This would result in 250 subjects in each vaccine group, and 125 subjects in placebo with the targeted total enrollment of 1125 subjects. The study will continue in a subpopulation of subjects among the US sites (N = 565) until 2 years after vaccination to collect long-term safety and immunogenicity data. At the time of writing this manuscript, the glycoprotein enzyme-linked immunosorbent assay (gpELISA) and the plaque-reduction neutralization titer test were still in the process of being validated, and the immunogenicity data of this study will be the subject of a separate manuscript.

Study Procedures

A vaccine report card (VRC) was distributed at visit 1 and reviewed with each subject. Injection-site reactions (including swelling, redness, and pain/tenderness) were recorded daily by the subject from days 1 to 5 postvaccination. Oral temperatures and systemic and/or injection-site adverse events (AEs) were recorded by the subject from days 1 to 42 postvaccination. Arthralgia (joint pain), arthritis (joint swelling), rashes, and vesicular lesions (blisters) were prompted on the VRC to be recorded by the subject from days 1 to 42 postvaccination. From the end of visit 3 (day 42) through visit 4 (month 6), only serious AEs (SAEs) and recurrences of events of arthralgia/arthritis, rash, and/or vesicular lesions were collected. Safety was evaluated for all subjects through 6 months postvaccination, including 42 days of solicited AEs. AE intensity was to be assessed as mild (awareness of sign or symptom, but easily tolerated), moderate (discomfort enough to cause interference with usual activity), or severe (incapacitating with inability to work or do usual activity). Injection-site redness or swelling from the day of vaccination through day 5 postvaccination was evaluated by maximum size.

Subjects who experienced arthralgia, arthritis, rash, or vesicular lesions at any time through 42 days postvaccination were instructed to immediately contact the investigative site. Based on the symptoms, subjects were to be brought back for unscheduled examinations, to potentially include a dermatology or rheumatology consultation, and collection of specimens (synovial fluid, vesicular fluid, and skin biopsies) to be tested for the presence of the vaccine virus via real-time polymerase chain reaction (PCR; details are shown in the Supplementary Materials).

In accordance with principles of Good Clinical Practice, written informed consent was obtained from each participant prior to study entry. Additional consent was obtained for the collection of specimens at the rheumatology/dermatology site. The protocol was approved by the human studies committees at each research site. All study assessments were conducted in a blinded manner; unblinding occurred after database lock.

Population

Healthy subjects 18–65 years old were eligible for the study (inclusion/exclusion criteria are shown in the Supplementary Materials). Participants were advised to avoid pregnancy by means of appropriate contraceptive methods.

Vaccine

The rVSVΔG-ZEBOV-GP vaccine is a live attenuated recombinant vaccine (details are shown in the Supplementary Materials). Vaccine (3 consistency lots of rVSVΔG-ZEBOV-GP vaccine [2×10^7 pfu] and 1 lot of high-dose rVSVΔG-ZEBOV-GP vaccine [1×10^8 pfu]) was stored at ≤ –70°C with the vaccine thawed and administered within 15 minutes after thawing. Placebo (0.9% normal saline) was stored at room temperature. Subjects were vaccinated with 1.0 mL of study vaccine/placebo intramuscularly in the deltoid muscle of the nondominant arm using a 3.0-mL polypropylene syringe and 23-gauge needle.

Randomization

A double-blind/masking technique was used. The rVSVΔG-ZEBOV-GP vaccine and placebo were prepared and dispensed by an unblinded pharmacist or qualified trial site personnel. The subject, the investigator, and personnel involved in the vaccine administration or clinical evaluation were blinded. Treatment allocation/randomization occurred centrally using an interactive voice response system using a computer-generated,

site-balanced allocation schedule. Treatment allocation/randomization was stratified according to age (18–45 and 46–65 years).

Statistical Analysis

All randomized participants who were vaccinated and had safety follow-up were included in the safety analysis and included in the group for the treatment they actually received. The primary safety objective was to determine the safety and tolerability of rVSVΔG-ZEBOV-GP vaccine from 3 consistency lot groups (A, B, and C, each separately and combined) and the high-dose group through 42 days postvaccination. An exploratory objective examined the safety and tolerability for SAEs through 6 months postvaccination.

The AEs and fever profiles were described for the study vaccine after each vaccination and for the entire vaccination period. AEs are summarized with counts, percentages, and, when provided, exact 95% CIs (Clopper-Pearson method). Comparisons of rVSVΔG-ZEBOV-GP to placebo are reported with 95% CIs calculated using the Miettinen and Nurminen method [8]. Nominal *P* values were provided for informative purposes, not for hypothesis testing.

All data were fully reviewed, source document verified, and no data queries were outstanding at the time of the database lock. However, as this study is continuing until 2 years postvaccination, data are subject to change pending further information.

Sample Size and Power

The sample size for this study (planned 250 subjects per lot) was determined to show consistency of immunogenicity between the 3 lots of rVSVΔG-ZEBOV-GP with 99% power assuming 10% dropouts; the standard deviation on the log-scale of the gpELISA geometric mean titer (GMT) of 1 (estimated from 3 phase 1 studies); and the true gpELISA GMT ratio between any 2 lots of 1, and equivalence margins of 0.5-fold and 2.0-fold. With a planned sample size of 750 rVSVΔG-ZEBOV-GP (250 × 3 consistency lot groups) and 125 planned placebo subjects, there was 80% power to detect 4% vs 0% AEs, respectively.

RESULTS

Participant Accounting and Demographics

Overall, 1197 subjects were randomized 2:2:2:2:1 to receive either a single vaccination of 1 of 3 consistency lots of rVSVΔG-ZEBOV-GP (2×10^7 pfu), a high dose of rVSVΔG-ZEBOV-GP (1×10^8 pfu), or placebo. A total of 1194 (99.7%) subjects were vaccinated and 1138 (95.1%) completed the study (Figure 1). The reasons for the 56 discontinuations were as follows: lost to follow-up (35), withdrawal (18), death (2), and physician decision (1). The baseline characteristics were comparable among groups (Table 1).

Adverse Events

Safety follow-up information was obtained in 1183 of 1194 (99.1%) vaccinated subjects. Overall, 81%–85% of participants in the vaccine groups reported ≥1 AE postvaccination compared with 44% of placebo recipients (Table 2). In general, the proportion of participants reporting injection-site and systemic AEs were higher in the vaccine groups compared to the placebo group and similar between the vaccine groups. The incidence of injection-site related events was 70.8% vs 13.5% and the incidence of systemic AEs was 63.2% vs 35.6% in the vaccine and placebo groups, respectively (Table 2). Table 3 displays the proportion of subjects with VRC-prompted injection-site AEs (incidence >0% in ≥1 vaccination group) and Table 4 displays systemic AEs (incidence ≥4 subjects in ≥1 group; day 1 to month 6) that were statistically significantly different in ≥1 vaccine group from placebo. Most of these reports were mild to moderate in intensity. The percentage of subjects in the combined lots group, high-dose group, and placebo group with severe injection site–related events was 2.8%, 2.7%, and 0.0%, respectively, and for severe systemic AEs was 10.3%, 13.5%, and 1.5% respectively (Tables 3 and 4). Pain was the most frequent reported injection-site related event (up to 70%) and pyrexia the most common systemic event (up to 29%). Fever of any degree postvaccination was more common in the high-dose group (32.2% had fever ≥38.0°C and 4.3% ≥39.0°C) than the combined lots group (20.2% had fever ≥38.0°C and 3.2% ≥39.0°C), and both vaccine groups reported higher rates of fever as compared to the placebo group (0.8% had fever ≥38.0°C and 0.8% ≥39.0°C) (Table 5). All SAEs between day 1 and month 6 after vaccination are presented in Supplementary Table 1, and all systemic AEs with an incidence ≥2% in ≥1 group between day 1 and month 6 after vaccination are presented in Supplementary Table 2.

Rash, Arthritis, and Arthralgia

Higher rates of rash were observed in the combined lots group (3.8%) and high-dose group (3.8%) compared to the placebo group (1.5%), but the differences between groups did not reach statistical significance.

In total, 18 of 1050 (1.7%) cases of arthritis (Medical Dictionary for Regulatory Activities [MedDRA] preferred terms *arthritis* [n = 15], *monoarthritis* [n = 1], *osteoarthritis* [n = 1], and *polyarthritis* [n = 1]) were reported in the vaccine group and none in the placebo group. Most subjects with arthritis had ≥1 affected joint (12/18). Using a broader definition for arthritis by adding the MedDRA preferred terms *joint swelling* and *joint effusion*, the number of subjects with arthritis events increased to 51 (4.9%). Arthralgia and arthritis (broader definition) were reported at a statistically higher rate in the vaccine groups than in placebo recipients (Table 6). In the combined lots, high-dose, and placebo groups, the incidence of arthralgia

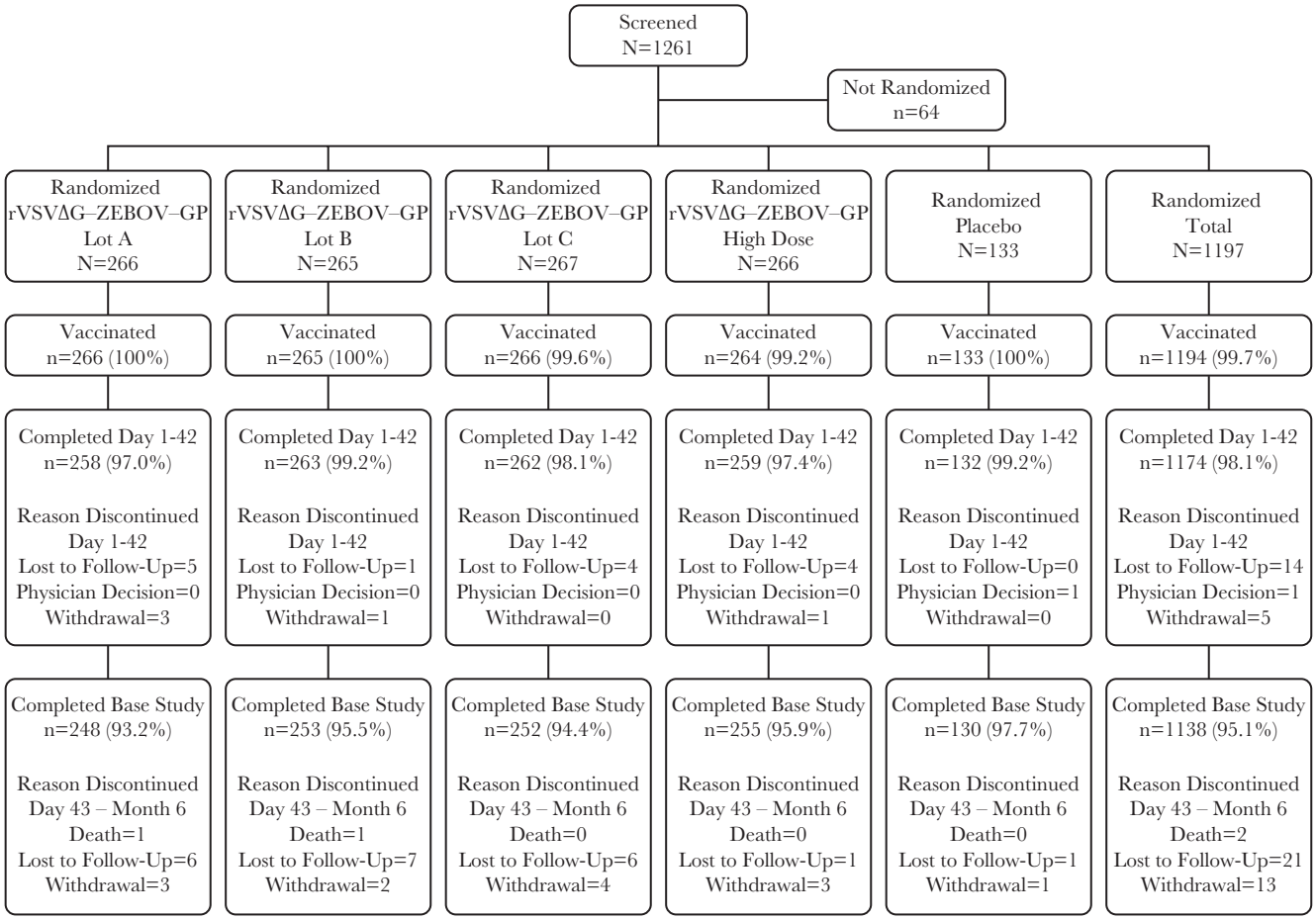

Figure 1. Study flowchart. Abbreviation: rVSVΔG-ZEBOV-GP, recombinant vesicular stomatitis virus–Zaire Ebola virus envelope glycoprotein vaccine.

was 17.1%, 20.4%, and 3.0%, respectively; and for arthritis was 5.1%, 4.2%, and 0%, respectively.

The onset of arthralgia was usually in the first week postvaccination (median, 2 days), of short duration (median, 3 days), and part of a syndrome of multiple early events such as fever, headache, and myalgia. The onset of arthritis was usually in the second week postvaccination (median, 11 days) with a median duration of 7 days. There was a notable difference in the incidence of arthritis (broader definition) between the age categories 18–45 and 46–65 years. It was most pronounced in the 2×10^7 group: 3.3% vs 7.5%, with a 95% CI for the difference (4.2%) of 0.7%–7.8%. The difference in the 1×10^8 pfu group was less pronounced (4.0% vs 4.6%). Combining all vaccine groups resulted in an arthritis incidence rate of 3.5% (18–45 years) vs 6.8% (46–65 years) with a 95% CI for the difference (3.4%) of 0.4%–6.3%.

Of 51 subjects with arthritis (broader definition), 8 (16%) also reported rash. One subject also reported dermatitis, and there were no cases of vasculitis. In some subjects with arthralgia/arthritis, rash, and/or vesicular lesions, laboratory samples were collected during the study if symptoms required further investigations.

Mild increases in C-reactive protein were noted in 22 subjects with these symptoms, and elevated alanine aminotransferase levels were observed in 4 subjects.

A total of 16 specimens were collected for the presence of rVSVΔG-ZEBOV-GP vaccine virus by PCR testing: 8 skin biopsies, 4 vesicular fluid, and 4 synovial fluid. Three specimens were positive (1 synovial fluid, 1 skin biopsy, and 1 vesicular fluid), 11 were negative, and 2 had an insufficient amount of sample to test. Details are presented in the Supplementary Materials.

The proportion of subjects reporting SAEs was low across all groups: 2.3% in the combined lots group, 1.2% in the high-dose group, and 0% in the placebo group (Table 2). There were no discontinuations due to vaccine-related SAEs.

Five pregnancies were reported during the first 42 days postvaccination. Two subjects were lost to follow-up, 2 subjects gave birth with no AEs or complications reported, and 1 subject had a spontaneous abortion. The estimated date of conception of the latter subject was 5 days postvaccination and the spontaneous abortion occurred 4 weeks after conception. The subject did not see a medical provider for the positive pregnancy test nor for the spontaneous abortion. No further information is available.

Table 1. Participant Characteristics (All Randomized Subjects)

Characteristic	rVSVΔG-ZEBOV-GP Lot A		rVSVΔG-ZEBOV-GP Lot B		rVSVΔG-ZEBOV-GP Lot C		rVSVΔG-ZEBOV-GP Combined Lots		rVSVΔG-ZEBOV-GP High Dose		Placebo	
Subjects in population	266		265		267		798		266		133	
Sex												
Male	123	(46.2)	130	(49.1)	129	(48.3)	382	(47.9)	117	(44.0)	61	(45.9)
Female	143	(53.8)	135	(50.9)	138	(51.7)	416	(52.1)	149	(56.0)	72	(54.1)
Age, y												
18–19	6	(2.3)	6	(2.3)	5	(1.9)	17	(2.1)	7	(2.6)	6	(4.5)
20–29	66	(24.8)	49	(18.5)	64	(24.0)	179	(22.4)	58	(21.8)	30	(22.6)
30–39	48	(18.0)	62	(23.4)	61	(22.8)	171	(21.4)	55	(20.7)	27	(20.3)
40–49	64	(24.1)	65	(24.5)	52	(19.5)	181	(22.7)	52	(19.5)	19	(14.3)
50–59	54	(20.3)	65	(24.5)	63	(23.6)	182	(22.8)	68	(25.6)	40	(30.1)
60–65	28	(10.5)	18	(6.8)	22	(8.2)	68	(8.5)	26	(9.8)	11	(8.3)
Mean (SD)	41.3	(13.4)	41.5	(12.4)	40.9	(13.1)	41.2	(13.0)	41.7	(13.4)	41.1	(13.7)
Range	18.0–65.0		18.0–65.0		18.0–65.0		18.0–65.0		18.0–65.0		18.0–65.0	
Race												
American Indian/ Alaska Native	2	(0.8)	2	(0.8)	0	(0.0)	4	(0.5)	0	(0.0)	1	(0.8)
Asian	0	(0.0)	1	(0.4)	3	(1.1)	4	(0.5)	2	(0.8)	3	(2.3)
Black	78	(29.3)	70	(26.4)	82	(30.7)	230	(28.8)	83	(31.2)	37	(27.8)
Multiple	3	(1.1)	4	(1.5)	7	(2.6)	14	(1.8)	2	(0.8)	1	(0.8)
Pacific Islander	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.8)	1	(0.8)
White	183	(68.8)	188	(70.9)	175	(65.5)	546	(68.4)	177	(66.5)	90	(67.7)
Weight at day 1, kg												
Mean (SD)	87	(24)	84	(21)	89	(24)	87	(23)	84	(20)	86	(24)
Range	42–192		40–193		44–216		40–216		49–164		41–195	
Body mass index, kg/m^2												
Subjects with data	263		264		265		792		264		133	
Mean (SD)	30	(8)	29	(7)	31	(8)	30	(8)	29	(7)	30	(7)
Range	18–70		16–59		17–62		16–70		16–55		18–57	

Data are presented as No. (%) unless otherwise indicated. All subjects were confirmed to be between 18 and 65 years of age; calculated age may be out of range due to age masking of date of birth. Lot A, B, C = 2×10^7 plaque-forming units (pfu); high dose = 1×10^8 pfu.

Abbreviations: rVSVΔG-ZEBOV-GP, recombinant vesicular stomatitis virus–Zaire Ebola virus envelope glycoprotein vaccine; SD, standard deviation.

Two subjects died during the study, both in the combined lots group. Neither death was considered by the investigator to be related to study vaccinations. A 64-year-old woman died of a craniocerebral injury after a fatal fall 152 days postvaccination, and a 47-year-old man died of hepatic failure with an onset 76 days postvaccination. The latter subject was diagnosed 7 years earlier with alcoholic pancreatitis and did not disclose this condition to the study site that inadvertently enrolled this subject in the study.

DISCUSSION

This phase 3, randomized, placebo-controlled clinical trial was designed to assess the safety and immunogenicity of 3 consistency lots (2×10^7 pfu) and a high-dose lot (1×10^8 pfu) of rVSVΔG-ZEBOV-GP vaccine in 1197 healthy adults. The immunogenicity data are currently not available and will be presented in a separate publication. The rVSVΔG-ZEBOV-GP vaccine was generally well-tolerated. A higher proportion of vaccine recipients than placebo recipients reported local reactogenicity including pain, erythema, and swelling as well as systemic reactogenicity including fever, headache, arthralgia, pain, chills, and fatigue. These events occurred principally during the first few days postvaccination. The proportion of participants reporting injection-site and systemic AEs were similar between all 4 vaccine groups. Pain was the most common local reactogenicity finding, occurring in up to 70% of subjects. Pyrexia was the most common systemic reactogenicity finding, occurring in up to 29% of subjects. The majority of AEs were of mild to moderate intensity and resolved within 1 week; no SAEs were associated with rVSVΔG-ZEBOV-GP vaccination. Arthralgia was reported by 20% of subjects receiving high-dose and 17% of subjects receiving low-dose vaccine. Arthralgia had a median onset within 2 days postvaccination, and lasted for a median of 3 days in the setting with other acute phase AEs such as fever, headache, and myalgia. Arthritis (broader term) was reported by 4.9% of all vaccinated subjects with a median onset of 10–11 days and duration of 5–7 days. Arthritis was reported more commonly in vaccinated subjects 46–65 years of age than subjects 18–45 years of age.

Table 2. Adverse Event Summary (Day 1 to Month 6), All Vaccinated Subjects

Adverse Event	rVSVΔG-ZEBOV-GP Lot A		rVSVΔG-ZEBOV-GP Lot B		rVSVΔG-ZEBOV-GP Lot C		rVSVΔG-ZEBOV-GP Combined Lots		rVSVΔG-ZEBOV-GP High Dose		Placebo	
Subjects in population with follow-up	264		263		263		790		260		133	
With ≥1 AEs	222	(84.1)	218	(82.9)	214	(81.4)	654	(82.8)	220	(84.6)	58	(43.6)
Injection site	188	(71.2)	196	(74.5)	190	(72.2)	575	(72.8)	181	(69.6)	18	(13.5)
Non–injection site	174	(65.9)	155	(58.9)	170	(64.6)	499	(63.2)	181	(69.6)	47	(35.6)
With no AE	42	(15.9)	45	(17.1)	49	(18.6)	136	(17.2)	40	(15.4)	75	(56.4)
With vaccine-related[a] AEs	213	(80.7)	211	(80.2)	209	(79.5)	633	(80.1)	211	(81.2)	31	(23.3)
Injection site	187	(70.8)	196	(74.5)	191	(72.6)	574	(72.7)	181	(69.6)	18	(13.5)
Non–injection site	145	(54.9)	130	(49.4)	145	(55.1)	420	(53.2)	159	(61.2)	19	(14.3)
With SAEs	7	(2.7)	4	(1.5)	7	(2.7)	18	(2.3)	3	(1.2)	0	(0.0)
With serious vaccine-related AEs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Who died	1	(0.4)	1	(0.4)	0	(0.0)	2	(0.3)	0	(0.0)	0	(0.0)
Discontinued[b] due to an AE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to a vaccine-related AE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to an SAE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to a serious vaccine-related AE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Data are presented as No. (%) unless otherwise indicated. Lot A, B, C = 2×10^7 plaque-forming units (pfu); high dose = 1×10^8 pfu.

Abbreviations: AE, adverse event; rVSVΔG-ZEBOV-GP, recombinant vesicular stomatitis virus–Zaire Ebola virus envelope glycoprotein vaccine; SAE, serious adverse event.

[a] Determined by the investigator to be related to the vaccine.

[b] Study medication withdrawn.

A number of phase 1 studies have reported safety findings in healthy volunteers who received doses of the rVSVΔG-ZEBOV-GP vaccine that ranged from 3×10^5 to 1×10^8 pfu [5–7]. Consistent with our findings, the most common AEs were injection-site pain, myalgia, headache, fatigue, fever, and chills. The majority of AEs were mild or moderate in intensity and no serious AEs were associated with rVSVΔG-ZEBOV-GP vaccination.

Table 3. Incidence and Intensity of Vaccine Report Card–Prompted Injection Site Adverse Events (Incidence >0% in 1 or More Vaccination Groups) Statistically Significantly Different in 1 or More Groups From Placebo (Day 1 to Month 6), All Vaccinated Subjects

	rVSVΔG-ZEBOV-GP Combined Lots			rVSVΔG-ZEBOV-GP Vaccine High Dose			Placebo	
Adverse Event	No.	% (95% CI)	% Difference vs Placebo (95% CI)	No.	% (95% CI)	% Difference vs Placebo (95% CI)	No.	% (95% CI)
Subjects in population with follow-up	790			260			133	
VRC-prompted injection site AEs	572	72.4 (69.1–75.5)	59.6 (52.3–65.3)	180	69.2 (63.2–74.8)	56.4 (47.8–63.8)	17	12.8 (7.6–19.7)
Total reported intensity	557	70.5		174	66.9		16	12.0
Mild intensity	386	48.9		103	39.6		16	12.0
Moderate intensity	149	18.9		64	24.6		0	0.0
Severe intensity	22	2.8		7	2.7		0	0.0
Pain	556	70.4 (67.1–73.5)	58.3 (51.1–64.0)	174	66.9 (60.8–72.6)	54.9 (46.3–62.2)	16	12.0 (7.0–18.8)
Total reported intensity	556	70.4		174	66.9		16	12.0
Mild intensity	385	48.7		103	39.6		16	12.0
Moderate intensity	149	18.9		64	24.6		0	0.0
Severe intensity	22	2.8		7	2.7		0	0.0

Every subject is counted a single time for each applicable specific injection-site AE. A subject with multiple injection-site AEs within a system organ class is counted a single time for that system organ class. A system organ class or specific injection-site AE appears on this report only if its incidence in 1 or more of the columns is greater than or equal to the percentage of incidence specified in the report title, after rounding. Erythema and swelling are not included in this table because they were measured by size instead of intensity

Abbreviations: AE, adverse event; CI, confidence interval; rVSVΔG-ZEBOV-GP, recombinant vesicular stomatitis virus–Zaire Ebola virus envelope glycoprotein vaccine; VRC, vaccine report card.

Table 4. Incidence and Intensity of Systemic Adverse Events (Incidence ≥4 Subjects in 1 or More Groups) Statistically Significantly Different in 1 or More Groups From Placebo (Day 1 to Month 6), All Vaccinated Subjects

	rVSVΔG-ZEBOV-GP Combined Lots			rVSVΔG-ZEBOV-GP Vaccine High Dose			Placebo	
Adverse Event	No.	% (95% CI)	% Difference vs Placebo (95% CI)	No.	% (95% CI)	% Difference vs Placebo (95% CI)	No.	% (95% CI)
Subjects in population with follow-up	790			260			133	
Systemic AEs	499	63.2 (59.7–66.5)	27.8 (18.8–36.2)	181	69.6 (63.6–75.2)	34.3 (24.1–43.7)	47	35.3 (27.3–44.1)
Mild intensity	187	23.7		62	23.8		29	21.8
Moderate intensity	231	29.2		84	32.3		16	12.0
Severe intensity	81	10.3		35	13.5		2	1.5
Pyrexia	168	21.3 (18.5–24.3)	20.5 (16.6–23.7)	76	29.2 (23.8–35.2)	28.5 (22.9–34.4)	1	0.8 (.0–4.1)
Mild intensity	105	13.3		46	17.7		1	0.8
Moderate intensity	51	6.5		24	9.2		0	0.0
Severe intensity	12	1.5		6	2.3		0	0.0
Headache	167	21.2 (18.3–24.2)	9.9 (2.9–15.2)	67	25.8 (20.6–31.5)	14.5 (6.4–21.8)	15	11.3 (6.5–17.9)
Mild intensity	69	8.7		28	10.8		11	8.3
Moderate intensity	74	9.4		30	11.5		4	3.0
Severe intensity	24	3.0		9	3.5		0	0.0
Arthralgia	138	17.5 (14.9–20.3)	14.5 (9.5–18.0)	53	20.4 (15.7–25.8)	17.4 (11.4–23.2)	4	3.0 (.8–7.5)
Mild intensity	63	8.0		23	8.8		3	2.3
Moderate intensity	69	8.7		22	8.5		1	0.8
Severe intensity	6	0.8		8	3.1		0	0.0
Pain[a]	86	10.9 (8.8–13.3)	9.4 (5.3–12.1)	33	12.7 (8.9–17.4)	11.2 (6.4–16.0)	2	1.5 (.2–5.3)
Mild intensity	42	5.3		7	2.7		2	1.5
Moderate intensity	35	4.4		24	9.2		0	0.0
Severe intensity	9	1.1		2	0.8		0	0.0
Chills	50	6.3 (4.7–8.3)	5.6 (2.0–7.7)	27	10.4 (7.0–14.7)	9.6 (5.5–14.1)	1	0.8 (.0–4.1)
Mild intensity	25	3.2		7	2.7		1	0.8
Moderate intensity	19	2.4		17	6.5		0	0.0
Severe intensity	6	0.8		3	1.2		0	0.0
Influenza-like illness	44	5.6 (4.1–7.4)	4.8 (1.3–6.9)	9	3.5 (1.6–6.5)	2.7 (–.9 to 5.8)	1	0.8 (.0–4.1)
Mild intensity	13	1.6		1	0.4		1	0.8
Moderate intensity	24	3.0		5	1.9		0	0.0
Severe intensity	7	0.9		3	1.2		0	0.0
Myalgia	40	5.1 (3.6–6.8)	4.3 (.8–6.3)	23	8.8 (5.7–13.0)	8.1 (4.1–12.3)	1	0.8 (.0–4.1)
Mild intensity	18	2.3		6	2.3		1	0.8
Moderate intensity	19	2.4		14	5.4		0	0.0
Severe intensity	3	0.4		3	1.2		0	0.0
Nausea	40	5.1 (3.6–6.8)	4.3 (.8–6.3)	14	5.4 (3.0–8.9)	4.6 (.9–8.2)	1	0.8 (.0–4.1)
Mild intensity	15	1.9		5	1.9		0	0.0
Moderate intensity	18	2.3		8	3.1		1	0.8
Severe intensity	7	0.9		1	0.4		0	0.0
Pain in extremity	26	3.3 (2.2–4.8)	3.3 (.5–4.8)	10	3.8 (1.9–7.0)	3.8 (1.0–6.9)	0	0.0 (.0–2.7)
Mild intensity	10	1.3		7	2.7		0	0.0
Moderate intensity	13	1.6		2	0.8		0	0.0
Severe intensity	3	0.4		1	0.4		0	0.0
Joint swelling	27	3.4 (2.3–4.9)	3.4 (.6–4.9)	9	3.5 (1.6–6.5)	3.5 (.6–6.5)	0	0.0 (.0–2.7)
Mild intensity	10	1.3		5	1.9		0	0.0
Moderate intensity	15	1.9		2	0.8		0	0.0
Severe intensity	2	0.3		2	0.8		0	0.0
Vomiting	13	1.6 (.9–2.8)	1.6 (–1.2 to 2.8)	8	3.1 (1.3–6.0)	3.1 (.2–6.0)	0	0.0 (.0–2.7)
Mild intensity	3	0.4		1	0.4		0	0.0
Moderate intensity	8	1.0		4	1.5		0	0.0
Severe intensity	2	0.3		3	1.2		0	0.0
Neck pain	11	1.4 (.7–2.5)	–1.6 (–6.1 to .5)	1	0.4 (.0–2.1)	–2.6 (–7.1 to .3)	4	3.0 (.8–7.5)
Mild intensity	4	0.5		1	0.4		3	2.3
Moderate intensity	6	0.8		0	0.0		1	0.8
Severe intensity	1	0.1		0	0.0		0	0.0

Every subject is counted a single time for each applicable specific injection-site AE. A subject with multiple injection-site AE within a system organ class is counted a single time for that system organ class. A system organ class or specific injection-site AE appears on this report only if its incidence in 1 or more of the columns is greater than or equal to the percentage incidence specified in the report title, after rounding.

Abbreviations: AE, adverse event; CI, confidence interval; rVSVΔG-ZEBOV-GP, recombinant vesicular stomatitis virus–Zaire Ebola virus envelope glycoprotein vaccine.

[a] The most reported verbatim term is "body aches."

Table 5. Maximum Temperatures (Days 1–42 Postvaccination), All Vaccinated Subjects

Temperature	rVSVΔG-ZEBOV-GP Combined Lots		rVSVΔG-ZEBOV-GP High Dose		Placebo	
Subjects in population, No.	797		264		133	
With temperature data (days 1–42), No.	788		258		132	
Maximum temperature (oral or oral equivalent)						
<38.0°C (100.4°F)	629	(79.8)	175	(67.8)	131	(99.2)
<39.0°C (102.2°F)	763	(96.8)	247	(95.7)	131	(99.2)
≥38.0°C (100.4°F)	159	(20.2)	83	(32.2)	1	(0.8)
≥39.0°C (102.2°F)	25	(3.2)	11	(4.3)	1	(0.8)
≥40.0°C (104.0°F)	4	(0.5)	1	(0.4)	0	(0.0)
≥41.0°C (105.8°F)	0	(0.0)	1[a]	(0.4)	0	(0.0)

Data are presented as No. (%) unless otherwise indicated. Percentages are calculated based on the number of subjects with temperature data. Multiple occurrences of maximum temperature are counted only once. Nonoral temperatures have been converted to oral equivalent.

Abbreviation: rVSVΔG-ZEBOV-GP, recombinant vesicular stomatitis virus–Zaire Ebola virus envelope glycoprotein vaccine.

[a]Maximum temperature was 41.1°C (106.0°F).

Arthritis was initially identified as an important reactogenicity event in 11 of 51 (22%) of subjects at a World Health Organization (WHO) site in Geneva, where 35 subjects were vaccinated with 1×10^7 pfu (18 open-label and 17 placebo-controlled) and 16 were vaccinated with 5×10^7 pfu (7 open-label and 9 placebo-controlled) [6, 7]. Of 11 subjects who reported arthralgia, 10 had undergone ultrasound or magnetic resonance imaging. Arthritis was diagnosed based on observed swelling on physical examination or effusion on imaging. Subsequent evaluation of arthritis in subjects vaccinated with 3×10^5 pfu (13 open-label and 38 placebo-controlled) indicated that 13 (25%) subjects reported arthralgia, 11 underwent imaging by ultrasound, and 12 (24%) had arthritis confirmed by clinical examination. Such a high proportion of subjects with arthritis was not observed, however, in the other phase 1 studies or at other WHO sites. No cases of arthritis were reported in a double-blind study conducted in the United States of 20 subjects vaccinated with 3×10^6 pfu and 20 subjects vaccinated with 2×10^7 pfu [5]. One case of arthritis each was reported in Hamburg, Germany, where 20 subjects were vaccinated and Kilifi, Kenya, where 40 subjects were vaccinated (50% at each site vaccinated with 3×10^6 pfu and 50% with 2×10^7 pfu in an open-label fashion). There were no cases of arthritis observed in Lambaréné (Gabon), where 39 subjects were vaccinated with either 3×10^6 pfu (n = 20) or 3×10^7 pfu (n = 19) [7].

The difference between the proportions of subjects reporting arthritis in this study (4.9%) compared to the Geneva study (22.5%) may be due to a more detailed clinical investigation combined with imaging to identify arthritis at the Geneva site, which was not performed in this study. The similar proportion of subjects with arthralgia (17.9%) in this study as described in the Geneva study (23.5%) supports this hypothesis. The median onset and duration of arthritis in this study was similar to the median onset (11 days) and duration (8 days) of arthritis at the Geneva site. The presence of rVSV RNA in synovial fluid in this and the Geneva study indicates seeding of rVSVΔG-ZEBOV-GP vaccine virus into joints. This suggests that at least some of the arthritis observed in this study could be classified as vaccine-induced arthritis. All but 2 subjects with arthritis recovered during the 6 months observation period. Those 2 subjects had existing degenerative osteoarthritis and still experienced some mild joint complaints at month 6. Rash was also reported with some degree of variability across studies. At the Geneva site, of the 11 subjects with arthritis who received either 1×10^7 pfu or 5×10^7 pfu of the vaccine, 3 (27%) reported a mild maculopapular rash, whereas of the 13 subjects with arthritis who received 3×10^5 pfu, 7 (54%) reported skin lesions that included rash [6, 7]. In our study, only 16% of the subjects with arthritis reported rash. The Geneva site also reported an age-dependent

Table 6. Specific Adverse Events Summary Days 1–42, All Vaccinated Subjects

Adverse Event	rVSVΔG-ZEBOV-GP Combined Lots		rVSVΔG-ZEBOV-GP High Dose		Placebo	
Subjects in population, No.	790		260		133	
Arthralgia, No. (%)	135	(17.1); $P < .001$	53	(20.4); $P < .001$	4	(3.0)
Day of onset, median (range)	2.0	(1–39)	2.0	(1–25)	5.5	(2–37)
Duration (d), median (range)	3.0	(0.0–113.0)	3.0	(0.1–37.0)	3.0	(2.0–26.0)
Arthritis[a], No. (%)	40	(5.1); $P = .008$	11	(4.2); $P = .016$	0	(0.0)
Day of onset, median (range)	11.0	(1–25)	10.0	(2–14)	0	(0)
Duration (d), median (range)	7.0	(0.4–44.0)	5.0	(1.0–156.0)	0	(0)
Rash[b], No. (%)	30	(3.8); $P = .181$	10	(3.8); $P = .202$	2	(1.5)
Day of onset, median (range)	7.5	(2–25)	10.5	(2–22)	3.5	(2–5)
Duration (d), median (range)	6.0	(0.4–50.0)	16.0	(4.0–29.0)	14.0	(7.0–21.0)

P values are presented for the comparison of the rVSVΔG–ZEBOV–GP vaccine groups vs placebo.

Abbreviation: rVSVΔG-ZEBOV-GP, recombinant vesicular stomatitis virus–Zaire Ebola virus envelope glycoprotein vaccine.

[a]Arthritis includes arthritis, polyarthritis, osteoarthritis, monoarthritis, joint swelling, joint effusion.

[b]Rash includes rash, rash macular, rash papular, rash vesicular, rash general (this adverse event [AE] was part of the group definition, but did not occur in the study population), petechia, purpura (this AE was part of the group definition, but did not occur in the study population).

effect on the incidence of arthritis. However, this was only observed in the low-dose groups (3×10^5 pfu) but not in the more comparable high-dose groups (1×10^7 or 5×10^7 pfu). In this larger study, the increased incidence of arthritis in the older age group (46–65) was observed in both the 2×10^7 pfu and 1×10^8 pfu groups.

Limitations to the interpretation of this study may include the fact that enrollment was restricted to subjects in North America and Europe, rather than Africa, where Ebola outbreaks have occurred and where the rVSVΔG-ZEBOV-GP vaccine is most likely to be utilized in future outbreaks. However, there are a number of ongoing rVSVΔG-ZEBOV-GP studies in Africa that will shed more light on the safety and immunogenicity in the target population such as (1) a randomized, double-blind, placebo-controlled trial (Partnership for Research on EBOV Vaccines in Liberia [PREVAIL]); (2) a randomized open-label trial to evaluate EBOV vaccine efficacy and safety in Guinea ("Ebola ça suffit"); and (3) a randomized open-label trial (Sierra Leone Trial to Introduce a Vaccine Against EBOV [STRIVE]) [9–12].

This is the first phase 3 study reporting a detailed safety profile of the clinical 2×10^7 pfu rVSVΔG-ZEBOV-GP dose. This is the dose used in the Guinea ring study in which a 100% (95% CI, 74.7%–100.0%) efficacy of the vaccine in preventing Ebola virus disease was observed [10].

In general, the rVSVΔG-ZEBOV-GP vaccine was well-tolerated, with increased rates of injection-site and systemic AEs compared to placebo observed in the lot consistency groups vaccinated with the clinical 2×10^7 pfu dose, as well as the group vaccinated with a higher dose of 1×10^8 pfu. There were no vaccine-related SAEs observed. The study supports the use of the rVSVΔG-ZEBOV-GP vaccine in persons at risk for Ebola virus disease.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. S. A. H., R. D., J. K. S., M. T. O., and F. A. H. drafted the initial manuscript. S. A. H., J. R. A., R. R., C. P. A., and L. C. participated in enrollment and data collection/acquisition, reviewed and revised the manuscript, and approved the final manuscript. S. A. H., R. D., J. K. S., M. T. O., K. L., and F. A. H. were involved with study concept/design, data analysis/interpretation, review and revision of the manuscript, and approval of the final manuscript.

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APPENDIX

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