Preclinical immunogenicity and efficacy of a vesicular stomatitis virus-based Sudan virus vaccine and an update on its performance in a phase 1 clinical trial.

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Abstract

Sudan virus (SUDV; species Orthoebolavirus sudanense) is responsible for outbreaks primarily in East Africa and to date, there have been 8 outbreaks caused by SUDV in South Sudan and Uganda. SUDV causes viral hemorrhagic fever in humans with fatality rates ranging from 41% to 100%. Unlike Zaire ebolavirus (EBOV), there are no licensed vaccines or therapeutics targeting SUDV, which highlights an urgent unmet need. IAVI is developing a SUDV vaccine based on a recombinant replication-competent vesicular stomatitis virus (rVSV) as used to develop ERVEBO®, the licensed single-dose ZEBOV vaccine produced by Merck (Figure 1). Here, we report on the preclinical immunogenicity and efficacy of the SUDV vaccine (rVSVΔG-SUDV-GP) in cynomolgus macaques and provide safety and immunogenicity results from a phase 1 clinical trial. In macaques, a single intramuscular (IM) injection of a research construct produced by IAVI protected up to 100% of animals challenged with SUDV Gulu variant 28 days post vaccination. All unvaccinated animals succumbed to infection by day 9. Anti-GP IgG ELISA titers were detectable in all vaccinated animals indicating that a single administration of rVSVΔG-SUDV-GP, even at the lowest dose, induced serum antibodies. Neutralizing antibodies evaluated by plaque reduction neutralization test (PRNT) based on rVSVΔG-SUDV-GP were detectable in 8/8 macaques vaccinated with 2x10E7 pfu, as well as 5/6 macaques vaccinated with 2x10E4 pfu. After demonstrating efficacy in macaques with IAVI research vaccine rVSVΔG-SUDV-GP, IAVI and its partners initiated a first-in-human phase 1 placebo-controlled, single-blind clinical trial (IAVI C108) at two U.S. sites using an investigational product rVSVΔG-SEBOV-GP manufactured by Merck. Safety and immunogenicity of a single IM injection was assessed in 36 healthy adult volunteers vaccinated with one single IM injection at three dose levels (Figure 2). There were no serious adverse events and most adverse events were transient, mild or moderate local reactions, and limited to local reactogenicity. All dose levels generated detectable humoral immune responses as measured by anti-GP IgG ELISA providing strong support for continued development of rVSVΔG-SEBOV-GP for vaccinating people at risk for SUDV infection.

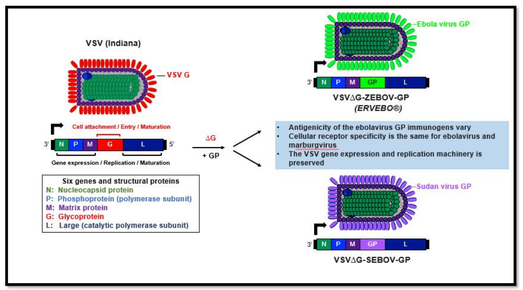

***Figure 1**. Structure of rVSV-based SUDV vaccine candidate.*

Study Group	rVSV-SEBOV (Merck product) Dosage (pfu), IM injection Day 1	Number of Participants Vaccine/Placebo
1	2 x 10E6	10/2
2	2 x 10E7	10/2
3	2 x 10E8	10/2
Total		36 (30/6)

***Figure 2**. IAVI C108, a placebo-controlled, single-blind safety trial with dose escalation utilizing the rVSVΔG-SEBOV vaccine.*

Objectives and phase 1 study design

To prepare for the future outbreaks, IAVI conducted a phase 1 clinical trial (IAVI C108) with SEBOV vaccine manufactured by Merck in June 2023 (Figure 2). This is a first-in-human, placebo-controlled, single-blind safety clinical trial that has been completed in February 2024. The trial was conducted at two U.S. sites with the same rVSVΔG-SEBOV-GP vaccine candidate that was shipped to Uganda for the 2022 outbreak. The duration of the trial was 6 months (from first subject first visit to last subject last visit). The objectives of IAVI C108 were as follows:

- **Primary endpoint**: To evaluate the safety and tolerability of rVSVΔG-SEBOV-GP vaccine.
- **Secondary endpoint:** To determine SUDV-GP-specific antibody responses induced by rVSVΔG-SEBOV-GP vaccine.

Results of the phase 1 trial and efficacy study in NHPs

Phase 1 results: The rVSVΔG-SEBOV-GP vaccine was safe and well tolerated across all dose levels. No Serious Adverse Events (SAEs) related to vaccination have occurred. Most participants experienced transient, mild or moderate local pain and tenderness. 5-12% participants from two highest dose groups experienced systemic reactions after vaccination, which resolved within a few days; moderate to severe systemic reactions of chills, headache, malaise, myalgia and diarrhea occurred more frequently at the higher dosage levels (Table 1). All vaccinated participants showed detectable IgG levels by day 28 after vaccination, with no statistically significant difference across the three dose groups: geometric mean of 217 EU/mL [95% CI 92.7–506] in the 2x10E6 PFU group, 289 EU/mL [95% CI 161–518] in the 2x10E7 group, and 355 EU/mL [95% CI 178–707] in the 2x10E8 PFU group. Neutralization activity was evaluated by PRNT method against SUDV was detected in 50% at day 28, 55% at day 84 and 59% at day 168 in a PRNT assay against vaccine strain and the related Gulu strain. Six months after vaccination, anti-SUDV-GP IgG were still detectable in all vaccinated volunteers without notable differences between groups (Figure 3).

NHP results: In macaques, a single IM injection of VSV-SUDV protected up to 100% of animals challenged with SUDV Gulu variant 28 days post vaccination; in contrast, controls succumbed on Day 9. Anti-GP IgG and IgM titers were detectable in all vaccinated animals on Day 10 and the titers on Day 26 were significantly elevated compared to the baseline. Neutralizing antibodies evaluated by plaque reduction neutralization test (PRNT) based on rVSVΔG-SUDV-GP were detectable in 8/8 macaques vaccinated with 2x10E7 pfu, as well as 5/6 macaques vaccinated with 2x10E4 pfu. The highest dose group 2x10E7 pfu demonstrated statistically significant titers compared to controls and the lowest dose group 2x10E2 (Figure 4).

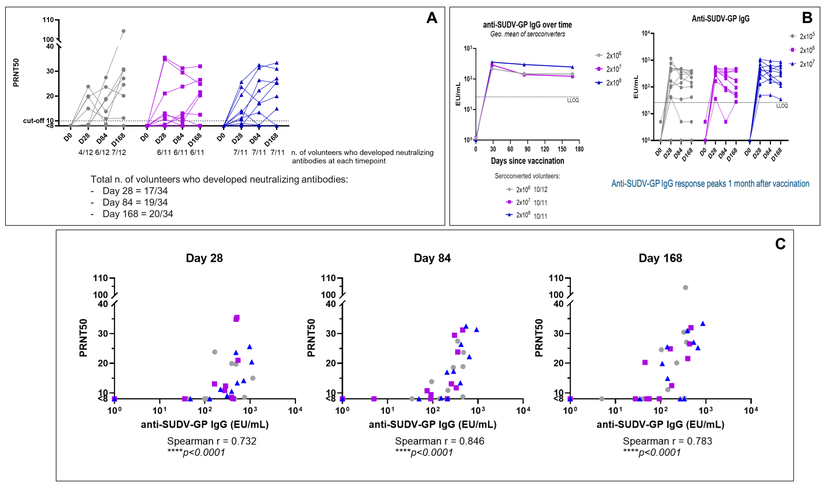

***Figure 3**. Immune response in participants following one vaccination at three dose levels. **A**. Neutralizing antibodies in vaccinees were developed on day 28 post immunization. **B**. IgG binding antibody response was at peak on day 28 and remained at this level through day 168. **C**. Binding and neutralizing antibodies correlated on days 28, 84 and 168 post vaccination.*

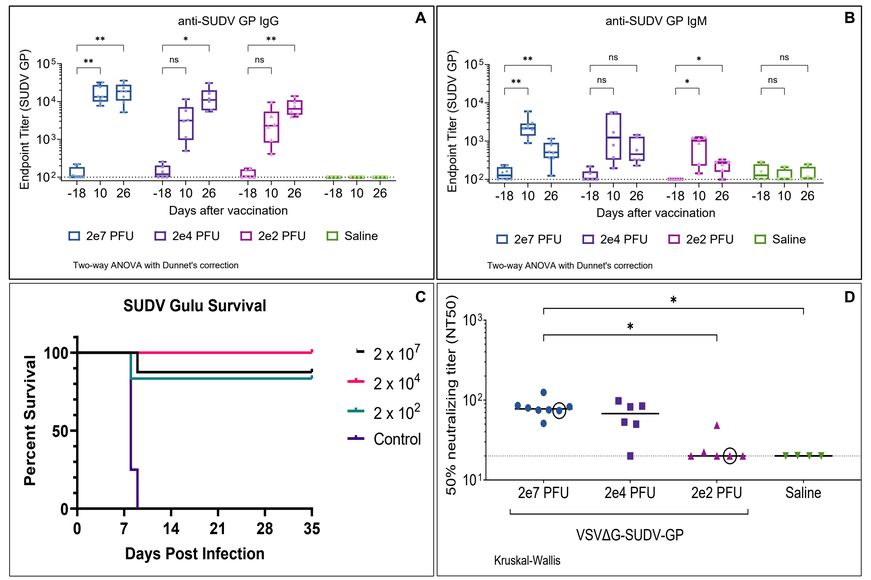

***Figure 4**. Immune response (measured by IgG and IgM ELISA and PRNT) in NHPs and survival following a single IM vaccination with rVSV-SUDV vaccine and a lethal Sudan Gulu variant challenge. **A and B.** Serum IgG GP and IgM GP antibodies were measured 10 days after vaccination in all groups. JPEO Gulu protein used as the coating antigen. An antibody response was demonstrated in all groups with a very limited dose response. **C**. NHP vaccination with a wide dose-range of VSVΔG-SUDV-GP protects NHPs against IM challenge with SUDV Gulu at 1000 pfu. **D**. Neutralizing antibodies titers were measured 26 days after vaccination. Similar neutralizing antibody responses observed from 10e7 to 10e4 PFU with limited detection of neutralization responses at low dose (200 PFU). Red circle indicates an animal that succumbed to infection. Plaque-reduction neutralization test based on neutralization of VSV-SUDV-GP vaccine virus (Sudan Boniface).*

Table 1. Overall Summary of Adverse Events.

Adverse Events	Placebo Group	rVSVΔG-SEBOV-GP Vaccine			Total
		Group 1: 2×10^6 pfu	Group 2: 2×10^7 pfu	Group 3: 2×10^8 pfu	All Vaccinated	
	(N=6) n(%)[m]	(N=10) n(%)[m]	(N=10) n(%)[m]	(N=10) n(%)[m]	(N=30) n(%)[m]	(N=36) n(%)[m]
Any AEs	6 (100.0) [35]	9 (90.0) [71]	9 (90.0) [130]	9 (90.0) [136]	27 (90.0) [337]	33 (91.7) [372]
Solicited AEs	5 (83.3) [34]	8 (80.0) [66]	9 (90.0) [127]	9 (90.0) [128]	26 (86.7) [321]	31 (86.1) [355]
Unsolicited AEs	1 (16.7) [1]	4 (40.0) [5]	3 (30.0) [3]	4 (40.0) [8]	11 (36.7) [16]	12 (33.3) [17]
Unsolicited AEs with Grade ≥ 2	0	1 (10.0) [1]	1 (10.0) [1]	4 (40.0) [5]	6 (20.0) [7]	6 (16.7) [7]
Solicited AEs with Grade ≥ 3	1 (16.7) [2]	0	2 (20.0) [5]	2 (20.0) [12]	4 (13.3) [17]	5 (13.9) [19]
Vaccine-related Unsolicited AEs	0	2 (20.0) [2]	1 (10.0) [1]	1 (10.0) [2]	4 (13.3) [5]	4 (11.1) [5]
Vaccine-related Unsolicited AEs with Grade ≥ 2	0	0	1 (10.0) [1]	1 (10.0) [2]	2 (6.7) [3]	2 (5.6) [3]
Severe AEs	0	0	0	0	0	0
Serious AEs	0	0	0	0	0	0
AEs of Special Interest	0	0	0	0	0	0
AEs Leading to Study Discontinuation	0	0	0	0	0	0
AEs Leading to Death	0	0	0	0	0	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of subjects in the study treatment group; n = Number of subjects in the study treatment group with an AE; m = number of all events; % = Percentage of subjects with an AE calculated as n/N * 100
Note(s): An AE was any untoward medical occurrence that started on or after the date of the study drug or started before the dose and worsened after the dose of study drug.
Note(s): Related AEs were defined as those assessed as possibly, probably, or definitely related to study drug, or those for which the relationship was unknown or missing.

Conclusions

The rVSVΔG-SEBOV-GP vaccine was safe and well tolerated in phase 1 clinical trial. No Serious Adverse Events (SAEs) related to vaccination occurred. Most participants experienced transient, mild or moderate local pain and tenderness. 5-12% participants in high dose groups experienced systemic reactions after vaccination, which resolved within a few days. Antibody responses were similar at all doses: GP-specific IgG antibodies were detected in all vaccinees 28 days after vaccination. Neutralization activity against SUDV was detected in 50% of participants at day 28, and antibodies persisted until day 168 post-vaccination. Binding and neutralizing antibodies correlated on days 28, 84 and 168 post vaccination. Results on efficacy in NHPs and safety in humans indicate that vaccine should be taken to further development and testing.

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