PharmaNote®

Vol. 35, Issue 8 May 2020 Established 1985

Ervebo© (ebola zaire vaccine, live/rVSVΔG -ZEBOV-GP); Post Epidemic Use Approval

Christopher R. Piszczatoski, PharmD

Ebola virus disease (EVD), formerly Ebola hemorrhagic fever and colloquially known as "Ebola," has made headlines in recent years with several outbreaks occurring, predominately in West Africa. It is caused by a filovirus that first appeared in 1976 as two concomitant outbreaks, one in South Sudan and the other in the Democratic Republic of the Congo.[1] The World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC) in response to a 2014 mass outbreak, which officially ended in 2016.[2] Since then, there have been three additional outbreaks in the Democratic Republic of the Congo, with one ongoing.3 Over 31,000 total cases of EVD have been identified and an estimated 13,000 deaths have occurred. Most (>90%) cases have been recorded since the 2014-2016 outbreak and have been attributed to the Zaire ebolavirus species.[3]

The virus spreads through direct contact with an infected person's body, fluids or clothes.[3] Symptoms typically appear in eight to ten days but can manifest anywhere from two to 21 days. Fever, aches, pains and fatigue, otherwise known as "dry" symptoms are the first to appear. Diarrhea and vomiting, known as the "wet" symptoms then manifest as the disease progresses. Diagnosis is possible based on the presence of symptoms and known exposure to EVD in the previous 21 days.[3] While often deadly, survivors are believed to have some immunity to the type of Ebola they endured.

Treatment is supportive, as there are currently no licensed agents for EVD.1 Patients are rehydrated via fluids and specific symptoms are treated as they appear. As part of the response to the 2014 PHEIC, vaccine development was accelerated. Two primary candidates emerged: the chimpanzee adenovirus 3-based vaccine (ChAd3-EBO-Z) and the recombinant vesicular stomatitis virus-based vaccine (rVSVΔG-ZEBOV-GP). A third vaccine is being studied with promising results consisting of an adenovirus type 26 vector vaccine encoding Ebola glycoprotein (Ad26.ZEBOV) and a modified vaccinia Ankara vector vaccine.[4]

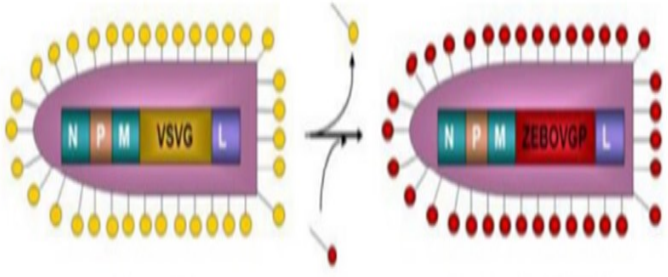
On December 19, 2019, Ervebo® (Ebola Zaire Vaccine, Live/rVSVΔG-ZEBOV-GP) was approved by the United States Food and Drug Administration (FDA) for the prevention of disease caused by Zaire ebolavirus in individuals aged 18 or older.[5] The purpose of this article is to review the safety and efficacy of Ervebo®.

Pharmacology

Mechanism of Action

Ervebo®, chemically known as rVSVΔG-ZEBOV-GP is a live, attenuated vaccine supplied as a 1mL, single-dose intramuscular injection. It is a recombinant, replication-competent vaccine consisting of a vesicular stomatitis virus (VSV) backbone that has been altered to express a glycoprotein from the Zaire ebolavirus in order to generate a host's neutralizing immune response to the Ebola Virus.[5] An illustration of this mechanism can be found in **Figure 1**.[6]

Figure 1 | Ervebo® Mechanism of Action[6]



IN THIS ISSUE

Clinical Trials

Eight phase I studies were conducted to assess safety and immunogenicity that are not reviewed in this article but were included in the FDA approval.[5] Based on these studies, it was determined that the vaccine was well tolerated and that a dose level of $2x10^7$ plaque forming units (pfu) was appropriate to proceed to phase II and III testing.[2] There were four phase II/III trials evaluating the safety, immunogenicity and efficacy of rVSVΔG-ZEBOV-GP that were considered in the FDA approval and are discussed in the following sections.[5] A summary of trials included for review can be found in **Table 1**.

PREVAIL I

Kennedy et al. conducted a phase III, randomized, double-blind, placebo-controlled trial at a single center in Monrovia, Liberia in 2015.[7] Study 1 (PREVAIL I) was originally designed to assess efficacy with a phase II subtrial embedded to assess safety and immunogenicity of both ChAd3 -EBO-Z and recombinant rVSVΔG-ZEBOV-GP compared to placebo. The incidence of EVD declined in Liberia during the study and the trial was subsequently altered to expand the safety subtrial and eliminate the efficacy component.

Patients were randomly assigned in a 2:1:2:1 ratio to receive an intramuscular injection of the ChAd3-EBO-Z vaccine (2 ml, at a concentration of 1×10^{11} pfu/mL), 2 ml of saline placebo, the rVSVΔG-ZEBOV-GP vaccine (1 ml, at a concentration of 2×10^7 pfu/mL), or 1 ml of saline placebo. Patients were excluded if they had a history of EVD, temperature greater than 38 degrees Celsius or were pregnant or breastfeeding. The primary safety outcome was grade 3 or 4 adverse events at one month and the primary immunogenicity outcome was positive immune response at one month.

There were 1500 patients that underwent randomization and were followed for 12 months with an attendance rate of 98.3%. Baseline demographics were similar among the three groups with median age 29.6 years, female sex 36.6% and HIV-positive status 5.2%. Patients had scheduled follow-up visits at week one, month one, month two and every two months thereafter to assess for adverse events and antibody response. Blood samples were drawn at baseline followed by week one and months one, six and 12. Samples were assessed for IgG antibodies against the Ebola surface glycoprotein via the Filovirus animal non-clinical group (FANG) assay. The median IgG antibody level against the Ebola virus was 78 enzyme-linked immunosorbent assay units (EU) per milliliter at baseline. Patients were considered to have a positive vaccine response if the log10 antibody titer was increased by a factor of four from baseline. No cases of EVD developed during the follow-up period.

STRIVE

Samai et al. conducted a randomized, unblinded phase II/III trial to evaluate the safety and efficacy of rVSVΔG-ZEBOV-GP in Sierra Leona in 2015.[8] No patients developed EVD during the course of the trial, making an efficacy assessment impossible. Thus only the safety of the vaccine was evaluated in the main protocol and with an additional detailed substudy.

Patients were randomized to an immediate vaccination (≤7 days of enrollment) or a deferred vaccination (≤ 18-24 weeks after enrollment). There was no placebo group. The study population consisted of frontline healthcare and response workers at least 18 years old. Patients were excluded if they had a history of EVD, were currently pregnant or breastfeeding, or had self-reported human immunodeficiency virus (HIV) or clinically important immunodeficiency.

There were 4,319 participants randomized to the immediate vaccination group and 4,332 to the deferred vaccination group, of which 4,165 and 3.833 respectively received vaccination for a total of 7,998 patients vaccinated. Demographics were similar across groups with median age 30.7 years, female sex 39.4% and predominately working as part of a frontline Ebola response worker (48.2%). Participants were monitored for six months after vaccination, with SAE occurrence as the primary safety endpoint. The safety substudy consisted of 449 patients and included telephone assessments on days one, three, seven, 14 and 28 after vaccination. Patients kept a daily symptom diary card, with endpoints of solicited injection-site and systemic reactions on vaccination day through day seven and solicited/unsolicited adverse events through day 28.

Halperin et al

From 2015-2016, Halperin et al. conducted a phase III randomized, double-blind, placebo-controlled trial to review the safety of rVSVΔG-ZEBOV-GP compared to placebo.[9] Healthy subjects aged 18 to 65 years old were eligible for enrollment. A total of 1,197 patients were randomized in a 2:2:2:2:1 ratio to receive one of three consistency lots of rVSVΔG-ZEBOV-GP vaccine at a dose of $2x10^7$ pfu, high dose vaccine of 1x108 pfu or saline placebo. Baseline characteristics were balanced across groups.

Participants were given a vaccine report card to record adverse events. Injection-site reactions were recorded daily from days one to five post-vaccination and oral temperatures, systemic reactions, injection-site reactions, arthralgia, arthritis, rashes and vesicular lesions were recorded days one through 42. After day 42, only serious adverse events and recurrences of either arthralgia, arthritis, rash and vesicular lesions were collected. A total of 1,194 patients were vaccinated and 1,138 completed the trial. The current data are reported for a six-month follow up period and results are reviewed in the safety subheading of the discussion section. The trial will include a two year follow up.

Ebola ça Suffit ("Ebola this is enough")

The efficacy of rVSVΔG-ZEBOV-GP was assessed by Henao-Restrepo et al. in a phase III open-label, cluster-randomized ring vaccination trial.[10] The trial took place during 2015-2016 outbreak in Guinea and parts of Sierra Leone.

Clusters were identified after index cases of EVD were confirmed. A list of contacts, and contacts of those contacts, was then generated including those around the index case who were at high risk via contact with the index case's body or fluids, linen or clothes. Patients were excluded if they had a history of EVD, experimental treatment in the past 28 days, anaphylaxis to a vaccine or component, serious disease requiring being confined to bed or hospital admission or were less than 18 years old, pregnant, or breastfeeding. Safety data for vaccine use in children emerged mid trial and the protocol was amended in August of 2015 to allow children as young as six years old to be included in the trial.

Patients were cluster-randomized on a 1:1 basis to either receive immediate vaccination or delayed vaccination 21 days later. Randomization only took place after clusters were identified, and was discontinued in July 2015 after interim analysis showed 100% vaccine efficacy. Patients thereafter were no longer randomized and received the vaccine immediately. Baseline characteristics that are reported (sex, age, various time from onset of symptoms to parameters and geographical location) are adequately balanced considering the cluster-based grouping. There were 117 index cases of EVD that were used to enumerate clusters, totaling 11,841 patients to be included in the trial. Of those clusters, 51 were randomized to immediate vaccination, 47 to delayed vaccination and 19 received immediate vaccination after randomization ended. Compliance with follow-up visits was greater than 80% for all groups. In the randomized portion of the trial, 34% of participants in both the immediate and delayed vaccination groups did not get vaccinated due to issues with consent or absenteeism.

The primary outcome was laboratory-confirmed EVD with onset ten or more days after randomization. Secondary outcomes included vaccine effect on deaths due to EVD. Safety was assessed via observation for 30 minutes post vaccination and at home visits on day three, week two, week six, week nine and week 12. Causality of adverse event to vaccination was judged by trial physicians.

Discussion

Safety

There was a safety component included in each of the four trials used for the approval of rVSVΔG-ZEBOV-GP.[7-10] In the PREVAIL I trial, six patients in the rVSVΔG-ZEBOV-GP group reported SAEs (1.2%).[7] Compared to placebo, there was no statistically significant difference in rates of SAEs (p=0.68). Over the full 12 month duration, SAEs occurred in 47 patients in the rVSVΔG-ZEBOV-GP group (9.4%) and 59 in the placebo group (11.8%). Malaria was noted to be the cause of 70% of all SAEs at one month and 71% at 12 months. The remainder of SAEs were varied in nature and reported only once or twice each. Headache, muscle pain, fever and fatigue were the most common adverse events occurring at increased rates in the active vaccination groups compared to placebo (P<0.001).

In the main protocol for STRIVE, there were 132 participants who reported at least one SAE (1.5%).[8] None of the SAEs reported were considered to be vaccine-related, and malaria accounted for approximately half. In the safety substudy (n=436), 91.2% of vaccinated patients reported systemic AEs within one week of vaccination compared to 35.5% in the unvaccinated group (p<0.001). These events were usually well-tolerated and self-limiting. Vaccinated patients reported more solicited adverse events of joint pain and rash compared to unvaccinated patients for days 5-28 post-vaccination (34% vs 11%, p<0.001; 16% vs 4%, p=0.003, respectively). Other solicited AEs such as joint swelling, skin vesicles and oral ulcers were not significantly different between groups.

Among vaccine groups in Halperin et al, 81-85% of patients reported at least one AE compared to 44% in the placebo group.[9] The most common AE's reported were systemic AEs, pyrexia, headache and arthralgia. Injection-site reactions were reported in 70.8% of vaccine groups compared to 13.5% in the placebo group and systemic AE's were reported in 63.2% of vaccine group participants compared to 35.6% of placebo patients. There were reports of SAEs across groups, but none were deemed as vaccine-related. Arthralgia and arthritis were reported at increased rates in both vaccine groups compared to placebo. Arthralgia was reported by 17.1% of patients in the combined lots group and 20.4% of patients in the high dose vaccine group compared to 3.0% of placebo patients (p>0.001 for both comparisons to placebo). Arthritis was reported by 5.1% of patients in the combined lots group and 4.2% of patients in the high dose group compared to no patients in the placebo group (p=0.008; p=0.016 for vaccine groups compared to placebo, respectively). The reports of rash were not signifi-

Table 1 | Trials Included for Review

Trial	Trial Type
Kennedy et al. (PREVAIL I)[7]	Phase II
Samai et al. (STRIVE)[8]	Phase II/III
Halperin et al.[9]	Phase III
Hanao-Restrapo et al. (Ebola ca Suffit)[10]	Phase III
NCT03031912[16]	Phase II
WHO Preliminary Results[17]	Unknown
Bolay et al.[18]	Phase II

Table 3 | Trials Demonstrating Antibody Response at One Month

Trial	Kennedy et al (PREVAIL)[7]		Bolay et al[17]
Trial Arm	**Placebo**	**rVSVΔG-ZEBOV-GP**	**rVSVΔG-ZEBOV-GP**
Median Baseline IgG Titer (IQR[a])	79 (50-148)	81 (49-141)	151 (99-241)
Responders at Baseline (%)	5.2	3.6	4.4
GMT[b] at 1 Week (95% CI)	87 (79-95)	92 (84-102)	-
Responders (%, 95% CI	1.4 (0.4-2.4)	2.4 (1.1-3.8)	-
GMT at 1 Month (95% CI)	87 (79-96)	1023 (928-1128)	1357 (1122-1641)
Responders (%, 95% CI)	2.6 (1.2-4.0)	81.5 (78.0-84.9)	77.3 (68.5-86.1)
GMT at 6 months 995% CI)	98 (89-109)	811 (746-881)	-
Responders (%. 95% CI)	5.4 (3.4-7.4)	75.7 (71.8-79.5)	-
GMT at 12 months (95% CI)	102 (92-111)	828 (762-889)	-
Responders (%, 95% CI)	6.8 (4.6-9.1)	76.5 (72.8-80.3)	-

[a]Interquartile range; [b]Geometric mean titer (EU/mL)

cantly different for either vaccine group when compared to placebo.

In the safety assessment of Henae-Restrapo et al, 53.9% of patients reported at least one adverse event in the 14 days after vaccination.[10] The most common reports were of headache, fatigue, arthralgia and muscle pain. Only 1.2% of patients reported a severe event, two of which (febrile reaction and influenza-like illness) were judged to be possibly vaccine-related.

The most commonly reported adverse events across trials were injection site reactions, fever, fatigue, rash, arthralgia and arthritis.[7-10] Live attenuated vaccines commonly cause injection site reaction, fever and fatigue. Rash development differed in significance between trials. Arthritis was noted to occur more often in elderly subsets, and STRIVE in particular may have had too small of a substudy population to observe rare events. There is an absence of long-term safety data in these STRIVE and Halperin et al. with durations of six months, but two-year data from Halperin et al. is forthcoming.[8,9] The concordance of safety data from these trials is that rVSVΔG-ZEBOV-GP is safe, with the most common adverse effects judged as mild and self-limiting.[7-10]

Immunogenicity

Immunogenicity of the vaccine was primarily assessed in PREVAIL I.[7] Positive antibody response at one month was increased in the at rVSVΔG-ZEBOV-GP group compared to placebo (83.7% vs 2.8%, $p<0.001$). This continued at twelve months, although positive response rates declined (79.5% vs 6.8%, $p<0.001$). There was no appreciable response at one week in any group. Findings were similar across subgroups of age, sex and previous contact with a person with EVD. Antibody response at one month in patients who were HIV positive was decreased with 61.9% having a positive response. There was no statistical analysis directly comparing ChAd3-EBO-Z to rVSVΔG-ZEBOV-GP, although ChAd3-EBO-Z had similar, albeit decreased, findings as rVSVΔG-ZEBOV-GP when compared to placebo.

It is unknown at what time between one week and one month that an immune response meets an immunogenic threshold. The three day interval represents an evidence gap between immunogenicity and efficacy data.[7,10] A limitation of this trial is that antibody responses were measured via FANG testing, with an arbitrary value of four times the baseline value considered a positive response. There are no established correlates of positive immunity to EVD after vaccination, although there are proposed variables that were not tested during the trials referenced.[11] Subsequently, over one third of patients vaccinated develop a T-cell mediated response with variable magnitudes, and results from recent subsets of patients involved in phase I trials show reproducible B-cell response.[12,13] The FANG assay has also since been validated to be an appropriate measure to assess immunogenicity of EBOV vaccines.[14]

Efficacy

Henao-Restrapo et al was the lone efficacy trial used for FDA approval.[10] On days 0-9 post-randomization in the immediate vaccination group, 20 cases of EVD were developed compared to 21 cases in the delayed vaccination group. No new cases developed from day 10 onward in the immediate vaccination group versus 23 total cases in eligible individuals in delayed clusters and those in the immediate clusters that were never vaccinated. Four of the cases occurred in patients who were vaccinated. Onset of EVD was within six days post vaccination, before an immunogenic response has developed as evidenced by other trials. The remaining 19 were never vaccinated. There were no new cases of EVD in any groups ten days or more post-vaccination. Efficacy of the rVSVΔG-ZEBOV-GP ten days

Table 3 | Trials Demonstrating Vaccine Efficacy[10,17]

Trial	Henao-Restrapo et al (Ebola ca Suffit)[10]	WHO Preliminary Results[17]
Trial Arm	**Immediate Vaccination (n=2,014)**	**All Vaccinated (n=68,279)**
EVD[a] with symptom development < 10 days post-vaccination	9	56
EVD with symptom development > 10 days post-vaccination	0	15
% Efficacy (95% CI)	100.0 (74.7-100.0)	97.5 (95.8-98.5)

[a]Ebola virus disease

or more post-vaccination was therefore estimated to be 100% (95% CI 79.3-100.0, p = 0.0033).

There are noted limitations for this trial. There is a lack of blinding and a placebo control in the trial. This is substituted with an immediate-vaccination and delayed-vaccination group. The 100% efficacy statistic drops to 75.1% when including all eligible adults at the cluster level and 76.3% when including all eligible and non-eligible participants, neither of which meet statistical significance. The medical teams conducting the trial did not stay in the communities that had delayed vaccination.[15] Their continuous contact with the immediate vaccination group may have had peripheral effects of lowering disease transmission via education and improved hygiene. There was no laboratory testing of participants at baseline, introducing the possibility of sub-clinical disease at trial onset. The primary analysis was delayed for ten days post-vaccination to account for the incubation period of the virus. However, the incubation period is 2-21 days.1 Baseline characteristics are poorly documented in the trial and cluster characteristics differ between trial arms.

Despite these limitations, focusing the trial on clusters around index cases instead of the population at large lends credence to real-world application. In addition, it would be unethical to withhold demonstrated immunogenic vaccines with a placebo control to those potentially at risk of a fatal disease during a current outbreak. The differences in size and characteristics of the clusters cannot be reasonably controlled as their determination is dependent upon purely societal factors. It can be dangerous to market this vaccine as 100% effective when those results may be skewed. Announcing it as a total barrier to disease may relax hygiene standards or use of protective clothing if populations believe they are protected.

Special Populations

There are gaps in special populations studied in this drug approval, notably pregnant women and children. While not actively recruited for ethical reasons, pregnancies did occur across trials. Loss of the fetus was noted to occur in approximately 20% of the 104 gestations in the STRIVE trial, but there is no data on statistics of pregnancy loss in the area available for comparison.[8] There were no congenital anomalies observed in the 38 births who attended a 28-day follow-up. Halperin et al's trial had five pregnancies, three of which the outcomes were known, and two had no abnormalities.[9] One was a spontaneous abortion, but the mother did not seek medical attention. While promising, these observations and the current data are ultimately insufficient to recommend routine use in pregnant women.

After review by an independent safety and monitoring board in Henae-Restrapo et al, randomization was stopped and immediate vaccination was also offered to children aged 6-17 years old, of which 194 received the vaccination.[10] There were no cases of EVD developed nor any safety concerns observed in this particular subset. As this is only observational data and this demographic is not well-studied, the vaccine is currently only indicated for use in patients 18 years or older.

Patients with human immunodeficiency virus (HIV) were only included in PREVAIL I as a population subset.[7] The vaccine appears to be safe in these patients as demonstrated by no SAEs at one month in any group, but with decreased immunogenicity possibly due to the immunocompromising nature of HIV itself. Interestingly as shown in PREVAIL I, patients vaccinated with either ChAd3-EBO -Z or rVSVΔG-ZEBOV-GP developed malaria at decreased rates compared to placebo (5.2% vs. 8.8%, P = 0.03; 6.6%, vs. 8.8%, P = 0.25, respectively). The authors note this may be due in part to cross-reactive immunity. A study evaluating the use of rVSVΔG-ZEBOV-GP in HIV-positive patients is currently ongoing in Canada.[16]

Additional Trials

There are two relevant trials not included in the FDA approval. A second ring-vaccination trial, not yet fully published, has since been conducted in the Democratic Republic of Congo.[17] Results from this trial are largely similar to Hanae-Restrapo et al. Of those that were vaccinated in the trial (n=68,279), there were 71 cases of EVD reported with 15 reporting symptom onset more than ten days after vaccination. There were nine deaths in those that developed

EVD within ten days of vaccination and no deaths after that duration. Vaccine efficacy was therefore calculated to be 97.5% (95% CI 95.8-98.5%). Although vulnerable to the same flaws as Ebola ca Suffit, this second trial can be taken as further evidence of the efficacy of rVSVΔG-ZEBOV-GP at preventing EVD due to the application and results in real world scenarios.

The PREVAIL I trial protocol was amended and approved for a single-arm cluster trial to assess safety and immunogenicity after an index case of EVD in a 15-year-old boy in Liberia in November 2015.[18] In this ring trial, 650 patients were identified as close contacts of the index case. Immunogenicity results from this trial were largely similar to the original PREVAIL I trial, with 77% of participants having a positive vaccine response at one month. Before vaccination, the median antibody level was 151 EU/mL (IQR 99-241), and one month after vaccination was 1339 EU/mL (1103-1626). Adverse events were similar to other reported trials. This lends further evidence to the use of antibody titers as a marker of immune response, rVSVΔG-ZEBOV-GP vaccine immunogenicity, and the safety profile of the vaccine itself.

Relevance to Patient Care

Ebola virus disease is highly infectious and often fatal. There have been multiple large outbreaks in the past five years, with no licensed treatments or vaccines. An effective vaccine could largely curtail current outbreaks and prevent further ones from occurring. This vaccine will likely not receive much use in the United States where prevalence of EVD is exceptionally low, but may see continued and routine use in the primarily affected regions in West Africa.

Conclusion

Ervebo® (rVSVΔG-ZEBOV-GP) is the first approved vaccine for the prevention of EVD. It has been largely used in the outbreaks in West Africa as part of the healthcare response. This FDA approval essentially legitimatizes the vaccine after years of use. While the trials used in the approval process are susceptible to certain methodological flaws, the accumulation of data shows the vaccine to be safe and likely effective for the general population in real world scenarios. Observational data is promising but currently insufficient to make recommendations for special populations of pregnancy, children and the immunocompromised. Further efficacy trials would be of use but may be difficult due to ethical limitations. Other vaccines are in development with promising results,. However, they are not yet widely used nor approved. At this time, Ervebo® is a viable option for those at risk of contracting EVD and should be utilized to its fullest extent at preventing and treating further outbreaks in affected regions.

References

1. Ebola Virus Disease [Internet]. Geneva: World Health Organization; c2020 [updated 2019 May 30, cited 2020 Jan 29]. Available from: https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease
2. Coller BG, Blue J, Das R et al. Clinical development of a recombinant Ebola vaccine in the midst of an unprecedented epidemic. Vaccine. 2017 Aug 16;35(35 Pt A):4465-4469. doi: 10.1016/j.vaccine.2017.05.097. Epub 2017 Jun 21
3. Ebola (Ebola Virus Disease) [Internet]. Atlanta: Centers for Disease Control and Prevention; c2020 [updated 2019 Nov 5, cited 2020 Jan 29]. Available from: https://www.cdc.gov/vhf/ebola/about.html
4. Milligan ID, Gibani MM, Sewell R et al. Safety and Immunogenicity of Novel Adenovirus Type 26- and Modified Vaccinia Ankara-Vectored Ebola Vaccines: A Randomized Clinical Trial. JAMA. 2016 Apr 19;315 (15):1610-23. doi: 10.1001/jama.2016.4218.
5. Ervebo® (Ebola Zaire Vaccine, Live/rVSVΔ-ZEBOV-GP) [Package Insert]. Whitehouse Statin, NJ: Merck & Co., Inc; Dec 2019
6. Assessment Report [Internet}. Amsterdam: European Medicines Agency; c2019 [updated 2019 Oct 17, cited 2020 Feb 1]. Available from: https://www.ema.europa.eu/en/documents/assessment-report/ervebo-epar-public-assessment-report_en.pdf
7. Kennedy SB, Bolay F, Kieh M et al. Phase 2 Placebo-Controlled Trial of Two Vaccines to Prevent Ebola in Liberia. N Engl J Med. 2017 Oct 12;377(15):1438-1447. doi: 10.1056/NEJMoa1614067.
8. Samai M, Seward JF, Goldstein ST et al. The Sierra Leone Trial to Introduce a Vaccine Against Ebola: An Evaluation of rVSVΔG-ZEBOV-GP Vaccine Tolerability and Safety During the West Africa Ebola Outbreak. J Infect Dis. 2018 May 18;217(suppl_1):S6-S15. doi: 10.1093/infdis/jiy020.
9. Halperin SA, Arribas JR, Rupp R et al. 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. J Infect Dis. 2017 Jun 15;215 (12):1789-1798. doi: 10.1093/infdis/jix189.
10. Henao-Restrapo A, Longini I, Egger M et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). Lancet. 2017 Feb 4;389(10068):505-518. doi: 10.1016/S0140-6736(16)32621-6. Epub 2016 Dec 23.
11. Rechtien A, Richert L, Lorenzo H et al. Systems Vaccinology Identifies an Early Innate Immune Signature as a Correlate of Antibody Responses to the Ebola Vaccine rVSV-ZEBOV. Cell Rep. 2017 Aug 29;20(9):2251-2261. doi: 10.1016/j.celrep.2017.08.023.

12. Poetsch JH, Dahlke C, Zinser ME et al. Detectable Vesicular Stomatitis Virus (VSV)-Specific Humoral and Cellular Immune Responses Following VSV-Ebola Virus Vaccination in Humans. J Infect Dis. 2019 Jan 29;219(4):556-561. doi: 10.1093/infdis/jiy565.
13. Ehrhardt SA, Zahner M, Krahling V et al. Polyclonal and convergent antibody response to Ebola virus vaccine rVSV-ZEBOV. Nat Med. 2019 Oct;25(10):1589-1600. doi: 10.1038/s41591-019-0602-4. Epub 2019 Oct 7.
14. Rudge TL Jr, Sankovich KA, Niemuth NA et al. Development, qualification, and validation of the Filovirus Animal Nonclinical Group anti-Ebola virus glycoprotein immunoglobulin G enzyme-linked immunosorbent assay for human serum samples. PLoS One. 2019 Apr 18;14(4):e0215457. doi: 10.1371/journal.pone.0215457. eCollection 2019.
15. Metzger W, Vivas-Martinez S. Questionable efficacy of the rVSV-ZEBOV Ebola vaccine. Lancet. 2018 March 17; 391(10125):1021. doi: 10.1016/S0140-6736(18) 30560-9
16. ClinicalTrials.gov [internet]. Bethesda: National Library of Medicine (US); c2020. Identifier NCT03031912, African-Canadian study of HIV-infected adults and a vaccine for Ebola; 2017 Jan 26 [cited 2020 Jan 29]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT03031912
17. Preliminary results on the efficacy of rVSV-ZEBOV-GP Ebola vaccine using the ring vaccination strategy in the control of an Ebola outbreak in the Democratic Republic of the Congo: an example of integration of research into epidemic response [Internet]. Geneva: World Health Organization; c2019 (updated 2019 Apr 12, cited 2020 Feb 1). Available from: https://www.who.int/csr/resources/publications/ebola/ebola-ring-vaccination-results-12-april-2019.pdf
18. Bolay F, Grandits G, Lane C et al. PREVAIL I Cluster Vaccination Study With rVSVΔG-ZEBOV-GP as Part of a Public Health Response in Liberia. J Infect Dis. 2019 May 15; 219(10): 1634–1641. ePub 2018 Dec 17. doi: 10.1093/infdis/jiy698

PharmaNote®

Published by the UF Family Practice Residency Program and the Departments of Community Health & Family Medicine and Pharmacotherapy & Translational Research

University *of* Florida