

PACKAGE INSERT

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ervebo solution for injection
Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP, live)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (1 mL) contains:

Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP^{1,2} live, attenuated) ≥ 72 million pfu³

¹Recombinant Vesicular Stomatitis Virus (rVSV) strain Indiana with a deletion of the VSV envelope glycoprotein (G) replaced with the Zaire Ebola Virus (ZEBOV) Kikwit 1995 strain surface glycoprotein (GP)

²Produced in Vero cells

³pfu= plaque-forming units

This product contains genetically modified organisms (GMOs).
This vaccine contains a trace amount of rice protein. See section 4.3.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
The solution is a colourless to slightly brownish-yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ervebo is indicated for active immunisation of individuals 18 years of age or older to protect against Ebola Virus Disease (EVD) caused by Zaire Ebola virus (see sections 4.2, 4.4 and 5.1).

The use of Ervebo should be in accordance with official recommendations.

4.2 Posology and method of administration

Ervebo should be administered by a trained healthcare worker.

Posology

Individuals 18 years of age or older: one dose (1 mL) (see section 5.1).

The need for a booster dose has not been established.

Paediatric population

The safety, immunogenicity and efficacy of Ervebo in children aged 1 to 17 years have not yet been established (see sections 4.8 and 5.1).

Method of administration

For precautions to be taken before administering the vaccine, see section 4.4.

For precautions regarding thawing, handling and disposal of the vaccine, see section 6.6.

Ervebo should be administered by the intramuscular (IM) route. The preferred site is the deltoid area of the non-dominant arm or in the higher anterolateral area of the thigh. Do not inject the vaccine intravascularly. No data are available for administration via the subcutaneous or intradermal routes.

Cover the vaccination injection site or any vesicles with an adequate bandage (e.g. any adhesive bandage or gauze and tape) that provides a physical barrier to protect against direct contact (see sections 4.4 and 5.3). The bandage may be removed when there is no visible fluid leakage.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 or to rice protein listed in section 2.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

Close monitoring is recommended following vaccination for the early signs of anaphylaxis or anaphylactoid reactions. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

Duration of protection

Vaccination with Ervebo may not result in protection in all vaccinees. Vaccine efficacy has been established in the period ≥ 10 to ≤ 31 days after vaccination, however the duration of protection is not known (see section 5.1). **The use of other Ebola control measures should therefore not be interrupted.**

Vaccination of contacts of Ebola cases should occur as soon as possible (see section 5.1).

Standard precautions when caring for patients with known or suspected Ebola disease

Vaccination with Ervebo does not eliminate the necessity of standard precautions when caring for patients with known or suspected Ebola disease. **All healthcare workers and other ancillary providers who have been vaccinated should not alter their practices with regard to safe injection, hygiene, and personal protective equipment (PPE) after vaccination.**

Healthcare workers caring for patients with suspected or confirmed Ebola virus should apply extra infection control measures to prevent contact with the patient's blood and body fluids and contaminated surfaces or materials such as clothing and bedding. Samples taken from humans and animals for investigation of Ebola infection should be handled by trained staff and processed in suitably equipped laboratories.

Vaccine administrators should counsel vaccinees to continue to protect themselves with adequate measures.

Immunocompromised individuals

Safety and efficacy of Ervebo have not been assessed in immunocompromised individuals. Immunocompromised individuals may not respond as well as immunocompetent individuals to Ervebo. As a precautionary measure, it is preferable to avoid the use of Ervebo in individuals with known immunocompromised conditions or receiving immunosuppressive therapy, including the following conditions:

- Severe humoral or cellular (primary or acquired) immunodeficiency, e.g. severe combined immunodeficiency, agammaglobulinemia, and AIDS or symptomatic HIV infection. A CD4+ T-lymphocyte count threshold for use in asymptomatic HIV-positive individuals has not been established.
- Current immunosuppressive therapy, including high doses of corticosteroid. This does not include individuals who are receiving topical, inhaled or low-dose parenteral corticosteroids (e.g. for asthma prophylaxis or replacement therapy).
- Diseases of the blood such as leukaemia, lymphomas of any type, or other malignant neoplasms affecting the haematopoietic and lymphatic systems.
- Family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.

Pregnant and breast-feeding women

As a precautionary measure, it is preferable to avoid the use of Ervebo during pregnancy. See section 4.6.

Transmission

Vaccine virus might be present in biological fluids such as blood, urine, saliva, semen, vaginal fluids, aqueous humor, breast milk, faeces, sweat, amniotic fluid, and placenta. Vaccine virus RNA has been detected by PCR in the plasma of most of the adult subjects. Vaccine virus RNA was mainly detected from Day 1 to Day 7. Shedding of vaccine virus has been detected by PCR in urine or saliva in 19 out of 299 adult subjects and in skin vesicles in 4 out of 10 adult subjects. The vaccine virus RNA was detected in a skin vesicle at 12 days post-vaccination in one of the four subjects.

Viral shedding was observed more frequently in children and adolescents compared to adults.

Transmission of vaccine virus through close personal contact is accepted as a theoretical possibility. Vaccine recipients should avoid close contact with and exposure of high-risk individuals to blood and bodily fluids for at least 6 weeks following vaccination. High-risk individuals include:

- Immunocompromised individuals and individuals receiving immunosuppressive therapy (see section above),
- Pregnant or breast-feeding women (see section 4.6),
- Children <1 year of age.

Individuals who develop vesicular rash after receiving the vaccine should cover the vesicles until they heal to minimise the risk of possible transmission of vaccine virus through open vesicles. Dispose of

contaminated bandages following institutional guidelines or WHO healthcare waste management policy. See section 5.3.

Inadvertent transmission of vaccine virus to animals and livestock is also theoretically possible, see below.

Individuals administered Ervebo should not donate blood for at least 6 weeks post-vaccination.

Transmission to animals and livestock

Transmission of vaccine virus through close contact with livestock is accepted as a theoretical possibility. Vaccine recipients should attempt to avoid exposure of livestock to blood and bodily fluids for at least 6 weeks following vaccination. Individuals who develop vesicular rash after receiving the vaccine should cover the vesicles until they heal. Dispose of contaminated bandages following institutional guidelines or WHO healthcare waste management policy. See section 5.3.

Concurrent illness

Vaccination should be postponed in subjects experiencing moderate or severe febrile illness. The presence of a minor infection should not result in deferral of vaccination.

Thrombocytopenia and coagulation disorders

The vaccine should be given with caution to individuals with thrombocytopenia or any coagulation disorder because bleeding or bruising may occur following an intramuscular administration in these individuals.

Protection against filovirus disease

The vaccine will not prevent disease caused by Filoviruses other than Zaire Ebola virus.

Impact to serological testing

Following vaccination with Ervebo, individuals may test positive for Ebola glycoprotein (GP) nucleic acids, antigens, or antibodies against Ebola GP, which are targets for certain Ebola diagnostic tests. Therefore, diagnostic testing for Ebola should target non-GP sections of the Ebola virus.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, and is considered to be essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

As there are no data on co-administration of Ervebo with other vaccines, the concomitant use of Ervebo with other vaccines is not recommended.

Immune globulin (IG), blood or plasma transfusions should not be given concomitantly with Ervebo. Administration of immune globulins, blood or plasma transfusions administered 3 months before or up to 1 month after Ervebo administration may interfere with the expected immune response.

It is unknown whether concurrent administration of antiviral medication including interferons could impact vaccine virus replication and efficacy.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited amount of data (less than 300 pregnancy outcomes) from the use of Ervebo in pregnant women, or women who became pregnant after receiving the vaccine. The safety of Ervebo has not been established in pregnant women.

As there are limitations to available data, including the small number of cases, caution should be exercised in drawing conclusions. Lack of reliable data on background rates of pregnancy and neonatal outcomes in the affected regions also makes a contextual assessment of the data challenging.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Ervebo during pregnancy. Nevertheless, considering the severity of EVD, vaccination should not be withheld when there is a clear risk of exposure to Ebola infection.

Pregnancy should be avoided for 2 months following vaccination. Women of child-bearing potential should use an effective contraceptive method.

Breast-feeding

It is unknown whether the vaccine virus is secreted in human milk.

A risk to the newborns/infants from breast-feeding by vaccinated mothers cannot be excluded.

Evaluation of the vaccine virus in animal milk has not been conducted. When Ervebo is administered to female rats, antibodies against the vaccine virus were detected in offspring, likely due to acquisition of maternal antibodies via placental transfer during gestation and via lactation. See section 5.3.

A decision must be made whether to discontinue breast-feeding or to abstain from Ervebo taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. In certain circumstances, where alternatives to breast-feeding are limited, the immediate need and health benefits to the infant should be taken into consideration and balanced with the mother's need for Ervebo. Both may present compelling needs that should be considered before vaccination of the mother.

Fertility

There are no data on fertility effects in humans.

Animal studies in female rats do not indicate harmful effects (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects of Ervebo on the ability to drive and use machines have been performed.

Ervebo has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Anaphylaxis was reported very rarely (0.006%) in clinical trials.

The most common injection-site adverse reactions were injection-site pain (70.3%), swelling (16.7%) and erythema (13.7%).

The most common systemic adverse reactions reported following vaccination with Ervebo were headache (36.9%), pyrexia (34.3%), myalgia (32.5%), fatigue (18.5%), arthralgia (17.1%), nausea (8.0%), chills (6.3%), arthritis (3.7%), rash (3.6%), hyperhidrosis (3.2%), and abdominal pain (1.4%). In general, these reactions were reported within 7 days after vaccination, were mild to moderate in intensity, and had short duration (less than 1 week).

Tabulated list of adverse reactions

Frequencies are reported as:

Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$), Very rare ($< 1/10,000$), Not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 1: Tabulated summary of adverse reactions considered related to vaccination

MedDRA-System Organ Class	Adverse Reactions	Frequency
Immune system disorders:	Anaphylactic reaction	Very Rare
Nervous system disorders:	Headache	Very common
Gastrointestinal disorders:	Abdominal pain Nausea	Common
Skin and subcutaneous tissue disorders:	Rash [§]	Common
Musculoskeletal and connective tissue disorders:	Arthralgia [§] Myalgia	Very common
	Arthritis [§]	Common
General disorders and administration site conditions:	Pyrexia Fatigue Injection site pain Injection site erythema Injection site swelling	Very common
	Chills Hyperhidrosis (sweats)	Common

[§]See description of selected adverse reactions.

Description of selected adverse reactions

Arthralgia and arthritis

Arthralgia was generally reported in the first few days following vaccination, was mild to moderate in intensity, and resolved within one week after onset. Arthritis (arthritis, joint effusion, joint swelling, osteoarthritis, monoarthritis or polyarthritis) was generally reported within the first few weeks following vaccination. In clinical trials with reports of arthritis, the median onsets were between 10 and 12 days (range from 0 to 25 days). Arthritis has been reported by subjects in clinical trials at a frequency that ranged from 0% in several protocols to 23.5% in one Phase 1 study. The majority of arthritis reactions were mild to moderate in severity. The median duration of arthritis across clinical trials in which arthritis was reported ranged from 2 days to 81.5 days (including duration of recurrent arthritis) with a maximum of 330 days. The reasons for differences in arthritis reporting across trials are not known but may be due to differences in study populations or outcome reporting. In the Phase 1 study with the highest rate of arthritis, 6 of 24 patients (25%) who reported arthritis after vaccination had persistent joint symptoms two years after vaccination. In a small number of subjects, the vaccine virus was recovered from joint effusion samples, suggestive of a virally-mediated process post-vaccination.

Rash

Rash was characterised in a variety of ways including generalised rash (2.3%), vesicular rash (0.5%), dermatitis (0.3%), or cutaneous vasculitis (0.01%) in clinical trials. In different trials, rash was reported with median onsets of 7.5 to 10.5 days (range from 0 to 47 days). The median durations reported were between 6 to 18 days. In 6 out of 18 subjects tested, the vaccine virus was detected in rashes (described as dermatitis, vesicles or cutaneous vasculitis lesions) suggesting a virally mediated process post-vaccination.

Transient decrease in white blood cells

Transient decreases in counts of lymphocytes, neutrophils and total white blood cells in the first 3 days following vaccination have been observed very commonly in Phase 1/2 studies; these events generally resolved after the first week post-vaccination. No adverse events of infections were observed in Phase 1/2 trials.

Paediatric population

Across the Phase 1 through Phase 3 trials, 234 children and adolescents 6 to 17 years of age received a dose of Ervebo.

The safety profile of Ervebo in children and adolescents 6 to 17 years of age was generally similar to that observed in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

No cases of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, Viral Vaccine, ATC code: J07BX02

Mechanism of action

Ervebo consists of a live, attenuated recombinant vesicular stomatitis virus-based vector expressing the envelope glycoprotein gene of Zaire Ebola virus (rVSVΔG-ZEBOV-GP). Immunisation of subjects with the vaccine results in an immune response and protection from Zaire Ebola Virus Disease (EVD). The relative contributions of innate, humoral and cell-mediated immunity to protection from Zaire Ebola virus are unknown.

Clinical immunogenicity and efficacy

The clinical development program included five Phase 2/3 (Protocols 009-012 and 018) clinical trials. All subjects received a single dose of vaccine.

Clinical efficacy

Clinical efficacy of Ervebo was assessed in Protocol 010.

Protocol 010 (Ring vaccination study) was a Phase 3 open-label cluster-randomised trial of ring vaccination (vaccinating contacts and contacts of contacts [CCCs] of index Ebola cases) which

evaluated efficacy and safety of Ervebo in Guinea. In this trial, 9,096 subjects ≥ 18 years of age who were considered CCCs of an index case with laboratory-confirmed EVD were randomised to immediate (4,539 subjects in 51 clusters) or 21 days delayed (4,557 subjects in 47 clusters) vaccination with Ervebo. Of those 9,096 subjects, 4,160 received Ervebo (2,119 subjects were vaccinated in the immediate arm and 2,041 subjects were vaccinated in the delayed arm). The median age of consenting CCCs was 35 years old. The final primary analysis included 2,108 subjects (51 clusters) vaccinated in the immediate arm and 1,429 subjects (46 clusters) eligible and consented on Day 0 in the delayed arm.

The final primary analysis was to assess efficacy against laboratory confirmed EVD by comparing incidence of cases occurring 10 to 31 days post-randomisation for those vaccinated in the immediate vaccination rings versus incidence of cases for subjects who consented on Day 0 in the delayed vaccination rings. Vaccine efficacy was 100% (unadjusted 95% CI: 63.5% to 100%; 95% CI adjusted for multiplicity: 14.4% to 100%) (0 cases in the immediate arm; 10 cases in 4 rings in the delayed arm). Randomisation was stopped after an interim analysis with a $p=0.0036$ that did not meet the pre-specified alpha level of 0.0027. Of the 10 cases, 7 were in contacts, and 3 in contacts-of-contacts. Uncertainties remain as to the level, duration and type of protection given the methodological limitations and the exceptional circumstances experienced during the trial.

Clinical immunogenicity

No immune correlates of protection have been defined.

Protocol 009 Partnership for Research on Ebola Vaccines in Liberia (PREVAIL) was a Phase 2 randomised, double-blind, placebo-controlled trial which evaluated the safety and immunogenicity of Ebola vaccine candidates including Ervebo. This trial compared Ervebo to normal saline placebo in 1,000 adults ≥ 18 years of age in Liberia.

Protocol 011 named Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE) was a Phase 2/3 randomised open-label trial which evaluated safety and immunogenicity of Ervebo in adults ≥ 18 years of age working in healthcare facilities or on frontline activities related to the Ebola response in Sierra Leone. In this trial, 8,673 adult subjects were enrolled and 8,651 with valid consents randomised to immediate (within 7 days of enrolment) or deferred (18 to 24 weeks after enrolment) vaccination with Ervebo. An immunogenicity sub-study included 508 subjects who were vaccinated and provided samples for the assessment of immunogenicity.

Protocol 012 was a Phase 3 randomised, double-blind, placebo-controlled trial which evaluated the safety and immunogenicity of three consistency lots and a high dose lot (approximately five times higher than the dose in consistency lots and dose used in other Phase 2/3 trials) of Ervebo compared to normal saline placebo. A total of 1,197 healthy subjects 18 to 65 years of age were enrolled in the US, Canada, and Spain.

Protocol 018 was a Phase 3 open-label trial conducted in Guinea to evaluate the safety and immunogenicity of Ervebo in vaccinated frontline workers 18 years of age and older that was implemented as Part B of the Phase 3 ring vaccination study for Protocol 010. In this trial, a total of 2,115 subjects were enrolled and 2,016 subjects were vaccinated with Ervebo. An immunogenicity sub-study included 1,217 subjects who were vaccinated and provided samples for the assessment of immunogenicity.

Immunogenicity testing has been performed in Protocol 009, Protocol 011, Protocol 012 and Protocol 018, and includes the assessment of binding immunoglobulin G (IgG) specific to purified Kikwit ZEBOV GP by validated enzyme linked immunosorbent assay (GP-ELISA) as well as validated neutralisation of vaccine virus by a plaque reduction neutralisation test (PRNT).

As shown in Tables 2 and 3, the geometric mean titers (GMT) of GP-ELISA and PRNT increased from pre-vaccination to post-vaccination. Over 93.8% of vaccine recipients met seroresponse criteria defined as a ≥ 2 -fold increase from baseline and ≥ 200 EU/mL at any time post-vaccination by GP-

ELISA and over 80.4% of subjects met seroresponse criteria defined as a ≥ 4 -fold increase from baseline at any time post-vaccination by PRNT. Over 80.1% of subjects continued to meet the seroresponse criteria for GP-ELISA and over 63.5% of vaccine recipients continued to meet seroresponse criteria for PRNT at 12 months. The clinical relevance of the immunogenicity data is currently not known.

Immunogenicity data were obtained in Protocol 009 in Liberia, Protocol 011 in Sierra Leone, Protocol 012 in the United States, Canada, and Europe, and Protocol 018 in Guinea. Gamma irradiation of specimens (from regions involved in Ebola outbreaks) was performed to reduce risk of wild-type Ebola virus infection of laboratory workers, but increased pre-vaccination GP-ELISA immune responses by approximately 20% and decreased post-vaccination GP-ELISA and PRNT immune responses by approximately 20%. Gamma irradiation, baseline seropositivity and other factors result in a higher immune response in Protocol 012.

Table 2. Summary of Geometric Mean Titers for the GP-ELISA from Protocols 009, 011, 012 and 018 Clinical Trials

Trial	Baseline GMT (n) [95% CI]	Month 1 GMT (n) [95% CI]	Month 6 GMT (n) [95% CI]	Month 12* GMT (n) [95% CI]	Month 24 GMT (n) [95% CI]
Protocol 009[§]	117.9 (464) [107.9, 128.7]	994.7 (475) [915.0, 1,081.3]	712.2 (477) [659.4, 769.3]	661.4 (475) [613.2, 713.4]	NA
Protocol 011[§]	92.7 (503) [85.3, 100.9]	964.3 (443) [878.7, 1,058.3]	751.8 (383) [690.6, 818.4]	760.8 (396) [697.6, 829.8]	NA
Protocol 012					
Combined Consistency Lots Group	< 36.11 (696) [<36.11, <36.11]	1,262.0 (696) [1,168.9, 1,362.6]	1,113.4 (664) [1,029.5, 1,204.0]	1,078.4 (327) [960.6, 1,210.7]	920.3 (303) [820.4, 1,032.3]
High Dose Group	< 36.11 (219) [<36.11, <36.11]	1,291.9 (219) [1,126.9, 1,481.2]	1,189.5 (215) [1,036.7, 1,364.9]	1,135.5 (116) [934.8, 1,379.3]	1,009.1 (105) [830.0, 1,226.7]
Placebo Group	< 36.11 (124) [<36.11, <36.11]	< 36.11 (124) [<36.11, <36.11]	< 36.11 (123) [<36.11, <36.11]	< 36.11 (65) [<36.11, <36.11]	< 36.11 (65) [<36.11, <36.11]
Protocol 018[§]	78.3 (1,123) [74.7, 82.0]	1,106.5 (1,023) [1,053.4, 1,162.2]	1,008.8 (75) [849.8, 1,197.6]	NA	NA
<p>The Full Analysis Set population was the primary population for the immunogenicity analyses in Protocols 009, 011 and 018 and consists of all vaccinated subjects with serology data and had a serum sample collected within an acceptable day range.</p> <p>The Per-Protocol Immunogenicity Population was the primary population for the immunogenicity analyses in Protocol 012 and includes all subjects who were compliant with the protocol, received vaccination, were seronegative at Day 1, and had a serum sample at one or more timepoints collected within an acceptable day range.</p> <p>n = Number of subjects contributing to the analysis.</p> <p>CI = Confidence interval; GP-ELISA = Anti-Glycoprotein Human Enzyme-Linked Immunosorbent Assay (EU/mL); GMT = Geometric mean titer</p> <p>*Protocol 011 from Month 9-12</p> <p>[§]Protocols 009, 011 and 018 used gamma irradiation of specimens to reduce risk of wild-type Ebola virus infection of laboratory workers</p>					

Table 3. Summary of Geometric Mean Titers for the PRNT from Protocols 009, 011, 012 and 018 Clinical Trials

Trial	Baseline GMT (n) [95% CI]	Month 1 GMT (n) [95% CI]	Month 6 GMT (n) [95% CI]	Month 12* GMT (n) [95% CI]	Month 24 GMT (n) [95% CI]
Protocol 009 [§]	< 35 (428) [<35, <35]	116.8 (477) [106.0, 128.8]	76.8 (477) [69.9, 84.4]	100.4 (476) [91.4, 110.3]	NA
Protocol 011 [§]	< 35 (438) [<35, <35]	116.0 (437) [105.7, 127.4]	95.3 (382) [86.3, 105.3]	119.9 (396) [107.9, 133.2]	NA
Protocol 012					
Combined Consistency Lots Group	< 35 (696) [<35, <35]	202.1 (696) [187.9, 217.4]	266.5 (664) [247.4, 287.0]	271.4 (327) [243.4, 302.7]	267.6 (302) [239.4, 299.2]
High Dose Group	< 35 (219) [<35, <35]	236.1 (219) [207.4, 268.8]	302.1 (215) [265.2, 344.1]	323.7 (116) [269.5, 388.8]	342.5 (105) [283.4, 414.0]
Placebo Group	< 35 (124) [<35, <35]	< 35 (123) [<35, <35]	< 35 (123) [<35, <35]	< 35 (65) [<35, <35]	< 35 (65) [<35, <35]
Protocol 018 [§]	< 35 (1,107) [<35, <35]	160.0 (1,024) [151.6, 168.9]	117.0 (75) [96.0, 142.6]	NA	NA
<p>The Full Analysis Set population was the primary population for the immunogenicity analyses in Protocols 009, 011 and 018 and consists of all vaccinated subjects with serology data and had a serum sample collected within an acceptable day range.</p> <p>The Per-Protocol Immunogenicity Population was the primary population for the immunogenicity analyses in Protocol 012 and includes all subjects who were compliant with the protocol, received vaccination, were seronegative at Day 1, and had a serum sample at one or more timepoints collected within an acceptable day range.</p> <p>n = Number of subjects contributing to the analysis.</p> <p>CI = Confidence interval; GMT = Geometric mean titer; PRNT = Plaque Reduction Neutralisation Test</p> <p>*Protocol 011 from Month 9-12</p> <p>§Protocols 009, 011 and 018 used gamma irradiation of specimens to reduce risk of wild-type Ebola virus infection of laboratory workers</p>					

Paediatric population

Efficacy in children has not been assessed. In a Phase 1 trial in children 6 to 17 years of age (median age = 10), non-validated ELISA and Pseudovirion Neutralisation Assay (PsVNA) results at Day 28 and Day 180 post-vaccination were similar to those observed in adults in the same study (see sections 4.4 and 4.8).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and toxicity to reproduction and development.

When Ervebo was administered to female rats, antibodies against the vaccine virus were detected in foetuses and offspring, likely due to trans-placental transfer during gestation and with the acquisition of maternal antibodies during lactation, respectively (see section 4.6).

Ervebo administered to female rats had no effects on mating performance, fertility, or embryonic/foetal development.

Ervebo administered to female rats had no effects on development or behaviour of the offspring.

Environmental Risk Assessment (ERA)

The vaccine virus is a Genetically Modified Organism (GMO). An ERA was conducted to determine the potential impact of this vaccine on human health and the environment. Because this vaccine is based on VSV, a known pathogen in livestock (e.g. horses, cattle, pigs), the risk assessment included species that are relevant for the wild type (wt) VSV backbone of this vaccine.

In a biodistribution study conducted in non-human primates, vaccine virus RNA was detected in lymphoid organs up to 112 days post-vaccination. However, infectious virus was detected at Day 1 and persistent infectious virus was not detected at any subsequent timepoints measured (Days 56, 84 and 112).

Based on limited shedding in adults, the results of a toxicity study in non-human primates, and lack of horizontal transmission in pigs, the overall risk of Ervebo to human health and the environment is considered negligible. However, as a precaution, vaccinees should attempt to avoid exposure of livestock to blood and bodily fluids for at least 6 weeks following vaccination to avoid the theoretical risk of spread of the vaccine virus. People who develop vesicular rash after receiving the vaccine should cover the vesicles until they heal. Cover the vaccination site or any vesicles with an adequate bandage (e.g. any adhesive bandage or gauze and tape) that provides a physical barrier to protect against direct contact with vesicle fluid (see section 4.2). The bandage may be removed when there is no visible fluid leakage. To avoid unintended exposure to livestock, ensure medical waste and other cleaning materials do not come in contact with livestock.

See sections 4.4 and 6.6 for further information.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Recombinant human serum albumin
Trometamol buffer
Water for injections
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store and transport frozen at -80°C to -60°C.

After thawing, the vaccine should be used immediately; however, in-use stability data have demonstrated that once thawed, the vaccine can be stored for up to 14 days at 2°C to 8°C prior to use. At the end of 14 days, the vaccine should be used or discarded. Upon removal from the freezer, the product should be marked with both the date that it was taken out of the freezer and also a new discard date (in place of the labelled expiry date). Once thawed, the vaccine cannot be re-frozen.

Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Solution for 1 dose in a vial (type I glass) with a stopper (chlorobutyl) and a flip-off plastic cap with aluminium seal.

Pack size of 10 vials.

6.6 Special precautions for disposal and other handling

- The vaccine is stored frozen at -80°C to -60°C and should be removed from the freezer and thawed in less than 4 hours until no visible ice is present. Do not thaw the vial in a refrigerator as it is not guaranteed that the vial will thaw in less than 4 hours. The thawed vial should then be gently inverted several times prior to withdrawal with the syringe. The vaccine should appear as a colourless to slightly brownish-yellow liquid with no particulates visible. Discard the vaccine if particulates are present.
- Withdraw the entire content of the vaccine from the vial using a sterile needle and syringe.

If feasible, the waste liquid from eye washes should be collected and decontaminated before discarding into the drain.

Any unused vaccine or waste material should be disposed in compliance with the institutional guidelines for genetically modified organisms or biohazardous waste, as appropriate.

If breakage/spillage were to occur, disinfectants such as aldehydes, alcohols and detergents are proven to reduce viral infection potential after only a few minutes.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

Package leaflet: Information for the user

Ervebo Solution for injection

Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP, live)

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are vaccinated because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your healthcare worker.
- If you get any side effects, talk to your healthcare worker. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ervebo is and what it is used for
2. What you need to know before you receive Ervebo
3. How Ervebo is given
4. Possible side effects
5. How to store Ervebo
6. Contents of the pack and other information

1. What Ervebo is and what it is used for

- Ervebo is a vaccine for adults who are 18 years of age and older.
- Ervebo is given to protect you from getting Ebola virus disease caused by the Zaire Ebola virus, which is a type of Ebola virus. This vaccine will not protect you against the other types of Ebola virus.
- Because Ervebo does not contain the whole Ebola virus, it cannot give you Ebola virus disease.

Your healthcare worker may recommend that you receive this vaccine in an emergency involving the spread of Ebola virus disease.

What is Ebola?

- Ebola is a serious disease caused by a virus. If you get Ebola, it can kill you. People catch Ebola from people or animals who are infected with Ebola or who died from Ebola.
- You can catch Ebola from blood and body fluids like urine, stools, saliva, vomit, sweat, breast milk, semen and vaginal fluids of people who are infected with Ebola virus.
- You can also catch Ebola from things that have touched the blood or body fluids of a person or animal with Ebola (like clothes or objects in direct contact).
- Ebola is not spread through the air, water or food.

Your healthcare worker will talk to you and then together you can decide if you should receive this vaccine.

2. What you need to know before you receive Ervebo

Do not receive Ervebo if you:

- are allergic to Ervebo, rice, or any of the other ingredients of this vaccine (listed in section 6). You should not receive Ervebo if any of the above apply to you. If you are not sure, talk to your healthcare worker.

Warnings and precautions

This vaccine might not protect everyone who receives it and the length of time you are protected from Ebola by Ervebo is not known.

Continue to follow your healthcare worker's recommendations to protect yourself from Ebola infection after you get this vaccine.

Hand washing:

Washing your hands correctly is the most effective way to prevent the spread of dangerous germs, like Ebola virus. It reduces the number of germs on the hands and so reduces their spread from person to person.

Proper hand washing methods are described below:

- Use soap and water when hands are soiled with dirt, blood, or other body fluids. There is no need to use antimicrobial soaps for washing hands.
- Use alcohol-based hand sanitiser when hands are not dirty. Do not use alcohol-based hand sanitiser when hands are soiled with dirt, blood, or other body fluids.

In an area affected by Ebola:

While in an area affected by Ebola, it is important to avoid the following:

- Contact with blood and body fluids (such as urine, faeces, saliva, sweat, vomit, breast milk, semen, and vaginal fluids).
- Items that may have come in contact with an infected person's blood or body fluids (such as clothes, bedding, needles, and medical equipment).
- Funeral or burial rituals that require handling the body of someone who died from Ebola.
- Contact with bats, apes and monkeys or with blood, fluids and raw meat prepared from these animals (bushmeat) or meat from an unknown source.
- Contact with semen from a man who had Ebola. You should follow safe sex practices until you know the virus is gone from the semen.

In case of rash:

If you get a rash where the skin is broken after receiving Ervebo, cover it until it heals. Put the used plasters and bandages in a sealed container, if possible, and throw them in the waste bin to make sure that people with a weak immune system or animals do not come into contact with the plasters and bandages.

Talk to your healthcare worker before you receive Ervebo if you:

Have had allergic reactions to vaccines or medicines

- If you have ever had an allergic reaction to a vaccine or medicine, talk to your healthcare worker before you receive this vaccine.

Have a weak immune system

If your immune system is weak (which means your body is less able to fight off diseases), you might not be able to receive Ervebo. You might have a weak immune system if:

- you have HIV infection or AIDS,
- you are taking certain medicines that make your immune system weak such as immunosuppressants or corticosteroids,
- you have cancer or a blood problem that makes your immune system weak,
- a member of your family has a weak immune system.

If you think you might have a weak immune system, ask your healthcare worker if you should receive this vaccine. If you do get the vaccine and have a weak immune system, the vaccine may not work as

well as in people with a normal immune system.

Are in contact with vulnerable individuals

Tell your healthcare worker if in the 6 weeks after you receive Ervebo you might be in close contact with or in the same household as:

- babies who are less than 1 year old,
- someone who may be pregnant or breast-feeding,
- someone who has a weak immune system.

This is because you could pass on the virus in the vaccine to them through your body fluids.

Plan to donate blood

- Do not donate blood for at least 6 weeks after you receive this vaccine.

Are in contact with farm animals

- Make sure your blood or body fluids do not come into close contact with farm animals for at least 6 weeks after you receive this vaccine. This is because of a possibility that you could pass on the virus in the vaccine to the animals.

Have a fever (high temperature)

- If you have a fever (high temperature), you should talk to your healthcare worker before receiving Ervebo. The vaccination may have to be delayed until your fever is gone.
- A minor infection such as a cold should not be a problem but talk to your healthcare worker before receiving Ervebo.

Have a bleeding disorder or bruise easily

- Tell your healthcare worker if you have a problem with bleeding or you bruise easily. Ervebo might make you bleed or bruise where the vaccine is injected.

Testing for Ebola after you receive Ervebo

- You may test positive for Ebola virus after you receive Ervebo. This does not mean that you have Ebola. Tell your healthcare worker that you have received Ervebo. Your healthcare worker might need to do another test.

Children and adolescents

If you or your child is under 18 years old, talk to your healthcare worker. It is not known if it is safe and works in children and adolescents.

Other medicines and Ervebo

Tell your healthcare worker if you are taking, have recently taken or might take any other medicines or vaccines.

No studies have looked at how other medicines or vaccines and Ervebo might interact with each other. Use of Ervebo with other vaccines is not recommended.

If you plan to receive blood or blood products

Do not receive this vaccine at the same time that you get blood or blood products. Ervebo might not work as well if you get blood or blood products 3 months before or up to 1 month after vaccination.

Pregnancy and breast-feeding

- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your healthcare worker for advice before you receive this vaccine. They will help you decide if you should receive Ervebo.
- Do not become pregnant for 2 months after you receive Ervebo. Women who are able to become pregnant should use an effective method of birth control. It is not known if Ervebo will harm you or your unborn baby. It is also not known if it can pass to your baby through your breast milk.

- If you might be in close contact with, or in the same household as someone who may be pregnant or breast-feeding during the 6 weeks after you receive Ervebo, tell your healthcare worker. This is because you could pass the vaccine to them through your body fluids.

Ervebo contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

3. How Ervebo is given

Ervebo is given by a healthcare worker. It is given as a single injection (dose of 1 mL) in the top of your arm or the outside of your thigh.

If you have any further questions on the use of this vaccine, ask your healthcare worker.

4. Possible side effects

Like all vaccines, Ervebo can cause side effects, although not everybody gets them.

Serious side effects:

Serious side effects are rare. Get medical care right away if you have symptoms of an allergic reaction, which may include:

- wheezing or trouble breathing,
- swelling of the face, lips, tongue, or other parts of the body,
- generalised itching, redness, flushing or itchy bumps on the skin.

Other side effects:

Very common (may affect more than 1 in 10 people):

- Headache,
- Joint pain,
- Muscle aches,
- Fever,
- Feeling tired,
- Pain, swelling, or redness at the injection site.

Common (may affect up to 1 in 10 people):

- Stomach pain,
- Nausea,
- Skin rash,
- Joint swelling,
- Chills,
- Excessive sweating.

Certain white blood cell counts can decrease below normal after vaccination but this decrease has not resulted in illness and the counts return to normal.

Most side effects go away within a few days. Joint pain and swelling may last for weeks or months in some people. In some people joint pain and swelling may come back after initially going away.

Tell your healthcare worker if you get any of the side effects listed above.

Additional side effects in children and adolescents

The vaccine has been studied in a small number of children and adolescents who were 6 to 17 years of

age. Overall, the side effects in children and adolescents were similar to those in adults.

Reporting of side effects

If you get any side effects, talk to your healthcare worker. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ervebo

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the vial label and the outer carton after 'EXP'. The expiry date refers to the last day of that month.
- Store and transport frozen at -80°C to -60°C.
- After thawing, the vaccine should be used immediately. However, once thawed, the vaccine can be stored for up to 14 days at 2°C to 8°C before use. Discard the vaccine if it is not used by the end of 14 days. Once thawed, the vaccine cannot be re-frozen.
- Upon removal from the freezer, the product should be marked with both the date that it was taken out of the freezer and also a new discard date (in place of the labelled expiry date).
- Keep the vial in the outer carton in order to protect from light.
- Do not use this vaccine if you notice particles in the liquid.
- Do not throw away any medicines via wastewater or household waste. Ask your healthcare worker how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ervebo contains

The active substance is a living Vesicular Stomatitis Virus. The surface protein of the virus has been replaced with that of Zaire Ebola Virus (rVSVΔG-ZEBOV-GP).

One dose (1 mL) contains:

Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP^{1,2} live, attenuated) ≥ 72 million pfu³

¹Recombinant Vesicular Stomatitis Virus (rVSV) strain Indiana with a deletion of the VSV envelope glycoprotein (G) replaced with the Zaire Ebola Virus (ZEBOV) Kikwit 1995 strain surface glycoprotein (GP)

²Produced in Vero cells

³pfu= plaque-forming units

This product contains genetically modified organisms (GMOs).

This vaccine contains a trace amount of rice protein.

This vaccine contains less than 1 mmol (23 mg) of sodium per dose.

The other excipients are recombinant human serum albumin, trometamol buffer, water for injections, hydrochloric acid, sodium hydroxide.

What Ervebo looks like and contents of the pack

- Ervebo is a solution for injection.
- Ervebo is a colourless to slightly brownish-yellow liquid.
- Ervebo is available in a pack of 10 vials.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

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The following information is intended for healthcare professionals only:

Standard precautions when caring for patients with known or suspected Ebola disease

Vaccination with Ervebo does not eliminate the necessity of standard precautions when caring for patients with known or suspected Ebola disease. **All healthcare workers, and other ancillary providers who have been vaccinated, should not alter their practices with regard to safe injection, hygiene, and personal protective equipment (PPE) after vaccination.**

Standard precautions, as outlined by WHO, include the following:

- Basic hand hygiene
- Respiratory hygiene
- Use of PPE (to block splashes or other contact with infected materials)
- Safe injection practices
- Safe burial practices

Healthcare workers caring for patients with suspected or confirmed Ebola virus should apply extra infection control measures to prevent contact with the patient's blood and body fluids and contaminated surfaces or materials such as clothing and bedding. When in close contact (within 1 metre) of patients with Ebola Virus Disease, healthcare workers should wear face protection (a face shield or a medical mask and goggles), a clean, non-sterile long-sleeved gown, and gloves (sterile gloves for some procedures).

Laboratory workers are also at risk. Samples taken from humans and animals for investigation of Ebola infection should be handled by trained staff and processed in suitably equipped laboratories.

Vaccine administrators should counsel vaccinees to continue to protect themselves with the following measures:

- Hand washing
- Avoid contact with blood and body fluids
- Safe burial practices
- Safe sex
- Avoid contact with bats and non-human primates or blood, fluids and raw meat prepared from these animals (bushmeat) or meat from an unknown source.

Instructions on the handling of the vaccine before administration

- Ervebo is stored frozen at -80°C to -60°C and should be removed from the freezer and thawed in less than 4 hours until no visible ice is present. Do not thaw the vial in a refrigerator as it is not guaranteed that the vial will thaw in less than 4 hours. The thawed vial should then be gently inverted several times prior to withdrawal with the syringe.
- After thawing, Ervebo should be used immediately; however, in-use stability data have demonstrated that once thawed, the vaccine can be stored for up to 14 days at 2°C to 8°C prior to use. At the end of 14 days, the vaccine should be used or discarded. Upon removal from the freezer, the product should be marked with both the date that it was taken out of the freezer and also a new discard date (in place of the labelled expiry date). Once thawed, the vaccine cannot be re-frozen.
- Ervebo is a colourless to slightly brownish-yellow liquid. Discard the vaccine if particulates are present.
- Ervebo should be administered intramuscularly. Do not inject the vaccine intravascularly. No data are available for administration via the subcutaneous or intradermal routes.
- Ervebo should not be mixed in the same syringe with any other vaccines or medicinal products.
- Withdraw the entire content of Ervebo from the vial using a sterile needle and syringe. The preferred injection site is the deltoid area of the non-dominant arm or in the higher anterolateral area of the thigh. Cover the injection site with gauze or bandage (e.g. any adhesive bandage or

gauze and tape) that provides a physical barrier to protect against direct contact with vesicle fluid. The bandage may be removed when there is no visible fluid leakage.

- Any unused vaccine or waste material should be disposed of in compliance with the institutional guidelines for genetically modified organisms or biohazardous waste, as appropriate. If breakage/spillage were to occur, disinfectants such as aldehydes, alcohols and detergents are proven to reduce viral infection potential after only a few minutes. If feasible, the waste liquid from eye washes should be collected and decontaminated before discarding into the drain.