▼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 pfu[3]
[1]Recombinant 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)
[2]Produced in Vero cells
[3]pfu= 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 1 year 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 1 year of age or older: one dose (1 mL) (see section 5.1).

Booster dose
The need and appropriate timing for booster dose(s) have not been established. Current available data are included in section 5.1.

Paediatric population
The posology in children 1 to 17 years of age is the same as in adults. Safety, immunogenicity and efficacy of Ervebo in children less than 1 year of age have not 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 in adults 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. In clinical trials, vaccine virus RNA has been detected by PCR in the plasma of most of the adult participants. 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 participants and in skin vesicles in 4 out of 10 adult participants. The vaccine virus RNA was detected in a skin vesicle at 12 days post-vaccination in one of the four participants.

In a Phase 1 study, vaccine viremia and viral shedding were observed more frequently (28/39) in children and adolescents 6 to 17 years of age compared to adults. In a subsequent Phase 2 study, 31.7% (19/60) of children and adolescents 1 to 17 years of age enrolled in a shedding sub-study shed vaccine virus in saliva following vaccination. Viral shedding was observed more frequently on Day 7 and declined thereafter, with no shedding detected at Day 56.

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.

Parents and caregivers of young vaccinees should observe careful hygiene especially when handling bodily waste and fluids for a minimum of 6 weeks after vaccination. Disposable nappies can be sealed in double plastic bags and disposed of in household waste. 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 individuals 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 are 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

For all age groups, anaphylaxis was reported very rarely (<1/10,000) in clinical trials.

In adults 18 years of age and older, the most common injection-site adverse reactions reported following vaccination with Ervebo were injection-site pain (70.3%), injection-site swelling (16.7%) and injection-site erythema (13.7%). The most common systemic adverse reactions were headache (55.1%), pyrexia (39.2%), myalgia (32.5%), somnolence, reduced activity, fatigue (25.5%), arthralgia (18.6%), chills (16.7%), decreased appetite (15.2%), abdominal pain (13.0%), nausea (9.5%), arthritis (3.7%), rash (3.6%), hyperhidrosis (3.2%), and mouth ulceration (2.2%). 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).

In children and adolescents 1 to 17 years of age, the most common injection-site adverse reactions reported following vaccination with Ervebo were injection-site pain (41.6%), injection-site pruritus (4.1%), injection-site swelling (3.0%) and injection-site erythema (0.5%). The most common systemic adverse reactions were pyrexia (62.2%), headache (45.7%), somnolence, reduced activity, fatigue (23.5%), decreased appetite (23.4%), myalgia (15.8%), dizziness (9.9%), crying (6.4%) and mouth ulceration (2.5%). In general, these reactions were reported within 7 days after vaccination and were mild to moderate in intensity.

Tabulated list of adverse reactions

Frequencies are reported as:
Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥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.

Individuals 1 year of age and older
Table 1 shows the adverse reactions considered as being at least possibly related to vaccination and observed in recipients of Ervebo.

For adults, the frequencies listed are based on the higher frequency reported in the Phase 2/3 placebo-controlled randomised trials, Protocol 009, Protocol 012 and Protocol 016, that have included a total of 2,143 individuals.

For children and adolescents, the frequencies listed corresponds to those observed in Protocol 016, a Phase 2 placebo-controlled randomised trial, that has included a total of 609 individuals (including 95 children from 1 to 3 years old, 310 children from 3 to 11 years old, and 204 children from 12 to 17 years old).

Table 1: Tabulated summary of adverse reactions in individuals 1 year of age and older considered related to vaccination

MedDRA-System Organ Class	Adverse Reactions	Frequency	
		Children and adolescents[¶]	Adults*
Immune system disorders:	Anaphylactic reaction	Very rare	Very rare
Nervous system disorders:	Headache	Very common	Very common
	Dizziness	Common	Common
Gastrointestinal disorders:	Abdominal pain	Very common	Very common
	Decreased appetite	Very common	Very common
	Nausea	Common	Common
Skin and subcutaneous tissue disorders:	Mouth ulceration	Common	Common
	Rash[§]	None	Common
Musculoskeletal and connective tissue disorders:	Arthralgia[§]	Common	Very common
	Myalgia	Very common	Very common
	Arthritis[§]	NA	Common
General disorders and administration site conditions:	Pyrexia	Very common	Very common
	Somnolence[†]	Very common	Very common
	Chills	Very common	Very common
	Crying	Common	NA[‡]
	Injection site pain	Very common	Very common
	Injection site erythema	Uncommon	Very common
	Injection site pruritus	Common	Common
	Injection site swelling	Common	Very common
	Hyperhidrosis (sweats)	Common	Common

[§]See description of selected adverse reactions.
[†]Includes: somnolence, reduced activity and fatigue.
[‡]NA (not applicable): not assessed for this population.
[¶]The adverse reactions of abdominal pain, nausea, rash, arthralgia, chills, and hyperhidrosis occurred with a difference of <5% between vaccine and placebo groups.
*The adverse reactions of dizziness and injection site pruritus occurred with a difference of <5% between vaccine and placebo groups.

Pyrexia was reported more frequently in younger children 1 to <3 years of age (83.2%), compared to children 3 to <12 years of age (64.8%), adolescents 12 to 17 years of age (48.3%) and adults (39.2%). Otherwise, the safety profile of Ervebo in children and adolescents 1 to 17 years of age was generally similar to that observed in adults.

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 participants 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 participants, 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 participants 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.

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 listed in Appendix V.

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 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 six Phase 2/3 clinical trials (Protocols 009, 012, 016 and 018). All participants received a single dose of vaccine except for a subset of participants in Protocol 002 (n=30) and Protocol 016 (n=399) who received two doses.

Clinical efficacy

Clinical efficacy of Ervebo in adults 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 participants ≥18 years of age who were considered CCCs of an index case with laboratory-confirmed EVD were randomised to immediate (4,539 participants in 51 clusters) or 21 days delayed (4,557 participants in 47 clusters) vaccination with Ervebo. Of those 9,096 participants, 4,160 received Ervebo (2,119 participants were vaccinated in the immediate arm and 2,041 participants were vaccinated in the delayed arm). The median age of consenting CCCs was 35 years old. The final primary analysis included 2,108

participants (51 clusters) vaccinated in the immediate arm and 1,429 participants (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 participants 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, named 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 participants 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 participants 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 participants 18 to 65 years of age were enrolled in the US, Canada, and Spain.

Protocol 016, named Partnership for Research on Ebola VACcination (PREVAC), was a Phase 2 randomised, double-blind, placebo-controlled trial which evaluated the safety and immunogenicity of Ervebo in participants who received: a single dose of Ervebo and normal saline placebo administered 56 days apart, two doses of Ervebo administered 56 days apart, or two doses of normal saline placebo. In this trial, 998 children and adolescents 1 to 17 years of age and 1,004 adults 18 years of age and older were enrolled in Guinea, Liberia, Mali and Sierra Leone.

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 participants were enrolled and 2,016 participants were vaccinated with Ervebo. An immunogenicity sub-study included 1,217 participants who were vaccinated and provided samples for the assessment of immunogenicity.

Immunogenicity data were obtained in Protocol 009 in Liberia, Protocol 011 in Sierra Leone, Protocol 012 in the United States, Canada, and Europe, Protocol 016 in Guinea, Liberia, Mali, and Sierra Leone, 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 glycoprotein enzyme-linked immunosorbent assay (GP-ELISA) immune responses by approximately 20% and decreased post-vaccination GP-ELISA and plaque reduction neutralisation test (PRNT) immune responses by approximately 20%. Samples from

Protocol 012 were not gamma irradiated. Absence of gamma irradiation, lower baseline seropositivity and other factors resulted in a higher immune response in Protocol 012.

Clinical immunogenicity in adults 18 years of age and older
Immunogenicity testing has been performed in Protocol 009, Protocol 011, Protocol 012, Protocol 016 and Protocol 018, and includes the assessment of binding immunoglobulin G (IgG) specific to purified Kikwit ZEBOV GP by validated GP-ELISA as well as validated neutralisation of vaccine virus by a PRNT.

As shown in Tables 2 and 3, the geometric mean titres (GMT) of GP-ELISA and PRNT increased from pre-vaccination to post-vaccination.

Over 93.8% of vaccine recipients from Protocols 009, 011, 012, 016 and 018 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 80.0% of participants met seroresponse criteria defined as a ≥4-fold increase from baseline at any time post-vaccination by PRNT. Over 80.3% of participants continued to meet the seroresponse criteria for GP-ELISA and over 63.8% of vaccine recipients continued to meet seroresponse criteria for PRNT at 12 months. The clinical relevance of the immunogenicity data is currently not known.

Table 2: Summary of geometric mean titres for the GP-ELISA in adults 18 years of age and older from Protocols 009, 011, 012, 016 and 018 clinical trials

Time point	GMT (n) [95% CI]				
	Protocol 009†	**Protocol 011†**	**Protocol 012‡**	**Protocol 016†**	**Protocol 018†**
Baseline	120.7 (487) [110.8, 131.5]	92.7 (503) [85.3, 100.9]	<36.11 (696) [<36.11, <36.11]	140.2 (379) [129.0, 152.4]	78.3 (1,123) [74.7, 82.0]
Month 1	999.7 (489) [920.1, 1,086.1]	964.3 (443) [878.7, 1,058.3]	1,262.0 (696) [1,168.9, 1,362.6]	1,241.2 (343) [1,116.4, 1,380.0]	1,106.5 (1,023) [1,053.4, 1,162.2]
Month 6	713.8 (485) [661.4, 770.3]	751.8 (383) [690.6, 818.4]	1,113.4 (664) [1,029.5, 1,204.0]	NA	1,008.8 (75) [849.8, 1,197.6]
Month 12§	664.3 (484) [616.5, 715.8]	760.8 (396) [697.6, 829.8]	1,078.4 (327) [960.6, 1,210.7]	1,088.4 (292) [983.5, 1,204.6]	NA
Month 24	766.3 (441) [705.0, 832.9]	NA	920.3 (303) [820.4, 1,032.3]	NA	NA
Month 36	755.7 (434) [691.6, 825.7]	NA	NA	NA	NA
Month 48	835.4 (400) [769.3, 907.2]	NA	NA	NA	NA
Month 60	785.9 (397) [722.3, 855.2]	NA	NA	NA	NA

The Full Analysis Set population was the primary population for the immunogenicity analyses in Protocols 009, 011 and 018 and consists of all vaccinated participants with serology data and had a serum sample collected within an acceptable day range.

The Per-Protocol Immunogenicity Population was the primary population for the immunogenicity analyses in Protocol 012 and includes all participants 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.

The Per-Protocol Immunogenicity Population was the primary population for the immunogenicity analyses in Protocol 016 and includes all vaccinated participants with serology data who were compliant with the protocol and had a serum sample collected within an acceptable day range.

n = Number of participants contributing to the analysis.

CI = Confidence interval; GP-ELISA = Glycoprotein Enzyme-Linked Immunosorbent Assay (EU/mL); GMT = Geometric mean titre

§Protocol 011 from Month 9-12

†Protocols 009, 011, 016 and 018 used gamma irradiation of specimens to reduce risk of wild-type Ebola virus infection of laboratory workers.

‡Combined consistency lots group

Table 3: Summary of geometric mean titres for the PRNT in adults 18 years of age and older from Protocols 009, 011, 012, 016 and 018 clinical trials

Time point	GMT (n) [95% CI]				
	Protocol 009†	**Protocol 011†**	**Protocol 012‡**	**Protocol 016†**	**Protocol 018†**
Baseline	<35 (451) [<35, <35]	<35 (438) [<35, <35]	<35 (696) [<35, <35]	17.5 (92) [16.7, 18.4]	<35 (1,107) [<35, <35]
Month 1	117.1 (490) [106.4, 128.9]	116.0 (437) [105.7, 127.4]	202.1 (696) [187.9, 217.4]	170.1 (98) [144.1, 200.7]	160.0 (1,024) [151.6, 168.9]
Month 6	76.7 (485) [69.8, 84.2]	95.3 (382) [86.3, 105.3]	266.5 (664) [247.4, 287.0]	NA	117.0 (75) [96.0, 142.6]
Month 12§	100.2 (485) [91.3, 110.0]	119.9 (396) [107.9, 133.2]	271.4 (327) [243.4, 302.7]	144.3 (84) [122.2, 170.4]	NA
Month 24	NA	NA	267.6 (302) [239.4, 299.2]	NA	NA

The Full Analysis Set population was the primary population for the immunogenicity analyses in Protocols 009, 011 and 018 and consists of all vaccinated participants with serology data and had a serum sample collected within an acceptable day range.

The Per-Protocol Immunogenicity Population was the primary population for the immunogenicity analyses in Protocol 012 and includes all participants 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.

The Per-Protocol Immunogenicity Population was the primary population for the immunogenicity analyses in Protocol 016 and includes all vaccinated participants with serology data who were compliant with the protocol and had a serum sample collected within an acceptable day range.

n = Number of participants contributing to the analysis.

CI = Confidence interval; GMT = Geometric mean titre; PRNT = Plaque Reduction Neutralisation Test

§Protocol 011 from Month 9-12

†Protocols 009, 011, 016 and 018 used gamma irradiation of specimens to reduce risk of wild-type Ebola virus infection of laboratory workers.

‡Combined consistency lots group

Paediatric population

Clinical immunogenicity in children and adolescents 1 to 17 years of age

As shown in Tables 4 and 5, the GMTs of GP-ELISA and PRNT increased from pre-vaccination to post-vaccination. In Protocol 016, 95.7% of participants met seroresponse criteria defined as a ≥2-fold increase from baseline and ≥200 EU/mL at any time post-vaccination by GP-ELISA and 95.8% of participants met seroresponse criteria defined as a ≥4-fold increase from baseline at any time post-vaccination by PRNT. At 12 months following vaccination, 93.2% of participants continued to meet the seroresponse criteria for GP-ELISA and 95.3% continued to meet seroresponse criteria for PRNT. Tables 4 and 5 provide a summary of GMTs for the GP-ELISA and for the PRNT, respectively, by age range.

Immune responses after vaccination with Ervebo in children and adolescents were non-inferior to those in adults at 1 month post-vaccination. The clinical relevance of the immunogenicity data is currently not known.

Table 4: Summary of geometric mean titres for the GP-ELISA in children and adolescents 1 to 17 years of age from Protocol 016 clinical trial

Age	Baseline GMT (n) [95% CI]	Month 1 GMT (n) [95% CI]	Month 12 GMT (n) [95% CI]
1 to <3 Years	50.2 (43) [40.2, 62.7]	1,192.1 (45) [827.6, 1,717.1]	1,719.3 (45) [1,245.7, 2,373.1]
3 to <12 Years	93.3 (180) [80.6, 108.1]	1,845.1 (171) [1,552.1, 2,193.4]	1,368.4 (153) [1,189.3, 1,574.5]
12 to 17 Years	140.0 (128) [120.9, 162.2]	2,103.3 (120) [1,772.2, 2,496.4]	1,451.6 (86) [1,188.6, 1,772.8]

The Per-Protocol Immunogenicity Population was the primary population for the immunogenicity analyses in Protocol 016 and includes all vaccinated participants with serology data who were compliant with the protocol and had a serum sample collected within an acceptable day range.
n=Number of participants contributing to the analysis.
CI=Confidence interval; GMT=geometric mean titre; GP-ELISA=glycoprotein enzyme-linked immunosorbent assay (EU/mL).
Protocol 016 used gamma irradiation of specimens to reduce risk of wild-type Ebola virus infection of laboratory workers.

Table 5: Summary of geometric mean titres for the PRNT in children and adolescents 1 to 17 years of age from Protocol 016 clinical trial

Age	Baseline GMT (n) [95% CI]	Month 1 GMT (n) [95% CI]	Month 12 GMT (n) [95% CI]
1 to <3 Years	17.5 (39) [<0, <0]	321.0 (33) [231.1, 445.7]	494.7 (32) [386.5, 633.3]
3 to <12 Years	17.9 (134) [16.9, 18.8]	280.4 (114) [241.3, 325.7]	312.7 (88) [271.0, 360.8]
12 to 17 Years	17.5 (111) [17.4, 17.6]	273.3 (119) [237.5, 314.6]	251.7 (85) [215.7, 293.7]

The Per-Protocol Immunogenicity Population was the primary population for the immunogenicity analyses in Protocol 016 and includes all vaccinated participants with serology data who were compliant with the protocol and had a serum sample collected within an acceptable day range.
n = Number of participants contributing to the analysis.
CI = Confidence interval; GMT = Geometric mean titre; PRNT = Plaque Reduction Neutralisation Test
Protocol 016 used gamma irradiation of specimens to reduce risk of wild-type Ebola virus infection of laboratory workers.

Clinical Immunogenicity in Participants Receiving a Booster Dose

Although an increase in antibody responses was observed in children and adolescents (n=195), and adults (n=194) after a second dose of Ervebo administered on Day 56 (Protocol 016), the increase in antibody titres was not maintained above the single dose regimen (n=386 children and adolescents, n=386 adults) at 12 months post-vaccination.

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 transient shedding data in adults and children from 1 year of age (n=5 for children from 1 to <3 years of age), 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 and caregivers should attempt to avoid exposure of livestock to blood and bodily fluids from vaccinees for at least 6 weeks following vaccination to avoid the theoretical risk of spread of the vaccine virus. For young vaccinees, if possible, soiled nappies can be cleaned with appropriate detergents or disinfectants; disposable nappies can be sealed in double plastic bags and disposed of in household waste for at least 6 weeks following vaccination. 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. 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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1392/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 November 2019
Date of latest renewal: 15 September 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.