

# ***Swiss Public Assessment Report*** ***Extension of therapeutic indication***

## **Ervebo, solution for injection**

**International non-proprietary name:** rVSVdeltaG-ZEBOV-GP, live, attenuated

**Pharmaceutical form:** solution for injection

**Dosage strength(s):** Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP live, attenuated) ≥72 million pfu in 1 mL of solution

**Route(s) of administration:** intramuscular (IM)

**Marketing authorisation holder:** MSD Merck Sharp & Dohme AG

**Marketing authorisation no.:** 68358

**Decision and decision date:** extension of therapeutic indication approved on 29.07.2024

### **Note:**

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

## Table of contents

<b>1</b>	<b>Terms, Definitions, Abbreviations .....</b>	<b>3</b>
<b>2</b>	<b>Background information on the procedure .....</b>	<b>4</b>
2.1	Applicant's request(s).....	4
2.2	Indication and dosage .....	4
2.2.1	Requested indication.....	4
2.2.2	Approved indication.....	4
2.2.3	Requested dosage .....	4
2.2.4	Approved dosage .....	4
2.3	Regulatory history (milestones).....	4
<b>3</b>	<b>Nonclinical aspects.....</b>	<b>5</b>
<b>4</b>	<b>Clinical aspects .....</b>	<b>5</b>
<b>5</b>	<b>Risk management plan summary .....</b>	<b>5</b>
<b>6</b>	<b>Appendix.....</b>	<b>5</b>

## 1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC <sub>0-24h</sub>	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C <sub>max</sub>	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
EVD	Ebola virus disease
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC <sub>50</sub>	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

## 2 Background information on the procedure

### 2.1 Applicant's request(s)

#### Extension(s) of the therapeutic indication(s)

The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

#### Authorisation as human medicinal product in accordance with Article 13 TPA

The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

### 2.2 Indication and dosage

#### 2.2.1 Requested indication

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

#### 2.2.2 Approved indication

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

#### 2.2.3 Requested dosage

##### Summary of the requested standard dosage:

Individuals 1 year of age or older: one dose (1 mL).

#### 2.2.4 Approved dosage

(see appendix)

### 2.3 Regulatory history (milestones)

Application	20 November 2023
Formal control completed	27 November 2023
List of Questions (LoQ)	25 March 2024
Response to LoQ	23 May 2024
Final decision	29 July 2024
Decision	approval

Swissmedic has not assessed the primary data (e.g. study reports) submitted with this application and relies for its decision on the assessment of the foreign reference authority, the EMA. This SwissPAR relates to the publicly available assessment report Ervebo (Procedure No. EMEA/H/C/004554/II/0025, Reference Number EMA/372877/2023, first published: 22.08.2023), issued by the EMA.

### 3 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The nonclinical aspects in this SwissPAR refer to the publicly available assessment report Ervebo (Procedure No. EMEA/H/C/004554/II/0025, Reference Number EMA/372877/2023, first published: 22.08.2023), issued by the EMA.

### 4 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The clinical aspects in this SwissPAR refer to the publicly available assessment report Ervebo (Procedure No. EMEA/H/C/004554/II/0025, Reference Number EMA/372877/2023, first published: 22.08.2023), issued by the EMA.

### 5 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.

The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

### 6 Appendix

#### Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Ervebo was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see [www.swissmedicinfo.ch](http://www.swissmedicinfo.ch)).

#### Note:

The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the «Undesirable effects» section for advice on the reporting of adverse reactions.

## **ERVEBO**

### **Composition**

#### *Active substances*

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

This product contains genetically modified organisms (GMOs).

#### *Excipients*

Recombinant human serum albumin

Trometamol buffer

Water for injections

Hydrochloric acid (for pH-adjustment)

Sodium hydroxide (for pH-adjustment)

This vaccine contains a trace amount of rice protein (see section «Contraindications»).

### **Pharmaceutical form and active substance quantity per unit**

Solution for injection

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

One dose (1 mL) contains:

Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP<sup>1,2</sup> live, attenuated) ≥72 million pfu<sup>3</sup>

<sup>1</sup>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)

<sup>2</sup>Produced in Vero cells

<sup>3</sup>pfu= plaque-forming units

### **Indications/Uses**

Ervebo is indicated for active immunization of individuals 1 year of age or older to protect against Ebola Virus Disease (EVD) caused by Zaire Ebola virus (see sections «Dosage/Administration», «Warnings and precautions» and «Properties/Effects»).

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

### **Dosage/Administration**

Ervebo should be administered by a trained healthcare worker.

#### *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.

### *Posology*

Individuals 1 year of age or older: one dose (1 mL) (see section «Properties/Effects»).

### *Booster dose*

The need and appropriate timing for booster dose(s) have not been established. Current available data are included in section «Properties/Effects».

### *Method of administration*

For precautions to be taken before administering the vaccine, see section «Warnings and precautions».

For precautions regarding thawing, handling and disposal of the vaccine, see section «Other information, Instructions for handling».

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 «Warnings and precautions» and «Preclinical data»). 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.

### *Elderly patients (older than 65 years)*

Across the Phase 1 through Phase 3 trials, 542 adults 65 years of age and older received a dose of Ervebo. Clinical studies of Ervebo did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects.

### *Children and adolescents*

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 «Undesirable effects» and «Properties/Effects»).

## **Contraindications**

Hypersensitivity to the active substances or to any of the excipients or to rice protein listed in section «Composition».

## **Warnings and precautions**

### *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. In the presented clinical studies, vaccine efficacy in adults has been evaluated in the period  $\geq 10$  to  $\leq 31$  days after vaccination, however the duration of protection is not known (see section «Properties/Effects»).

**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 «Properties/Effects»).

#### *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 instruct vaccinees to continue to protect themselves with adequate measures.

#### *Transmission of wild-type Ebola virus by vaccinated individuals.*

Data on the potential risk of transmission of wild-type Ebola virus by vaccinated individuals, who may be asymptomatic carriers of the virus has not been studied.

#### *Immunocompromised individuals*

Safety and efficacy of Ervebo have not been assessed in immunocompromised individuals. Immunocompromised individuals may respond inadequately to Ervebo compared to immunocompetent individuals. 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 and lactation. See section «Pregnancy, lactation».

#### *Transmission of the vaccine virus*

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 «Pregnancy, lactation»),
- 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 in accordance with local requirements. See section «Preclinical data».

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 «Preclinical data».

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 of the vaccine virus 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 in accordance with local requirements. See section «Preclinical data».

#### *Concurrent illness*

Vaccination should be postponed in individuals experiencing moderate or severe febrile illness.

#### *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.

#### *Arthritis*

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. See section «Undesirable effects».

#### *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, as these are detected in certain diagnostic tests for Ebola. Therefore, diagnostic testing of vaccinated individuals 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.

### **Interactions**

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. Administration of other vaccines should be avoided for 6 weeks following vaccination to avoid the possibility of interaction with this vaccine. 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.

### **Pregnancy, 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 «Preclinical data»).

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.

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

#### *Lactation*

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 «Preclinical data».

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 «Preclinical data»).

### **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 is not anticipated to have any influence on the ability to drive and use machines.

### **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 ( $\geq 1/10$ ), 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.

#### *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 <sup>¶</sup>	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 <sup>§</sup>	None	Common
Musculoskeletal and connective tissue disorders:	Arthralgia <sup>§</sup>	Common	Very common
	Myalgia	Very common	Very common
	Arthritis <sup>§</sup>	NA	Common
General disorders and administration site conditions:	Pyrexia	Very common	Very common
	Somnolence <sup>†</sup>	Very common	Very common
	Chills	Very common	Very common
	Crying	Common	NA <sup>‡</sup>
	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	

<sup>§</sup>See description of selected adverse reactions.

<sup>†</sup>Includes: somnolence, reduced activity and fatigue.

<sup>‡</sup>NA (not applicable): not assessed for this population.

<sup>¶</sup>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 of suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any new or serious suspected adverse reactions online via the EIViS portal (Electronic Vigilance System). You can obtain information about this at [www.swissmedic.ch](http://www.swissmedic.ch).

## **Overdose**

No cases of overdose have been reported.

## **Properties/Effects**

### *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 (rVSV $\Delta$ G-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.

### *Pharmacodynamics*

Not applicable.

### *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 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  $\geq 18$  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  $\geq 18$  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  $\geq 18$  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  $\geq 2$ -fold increase from baseline and  $\geq 200$  EU/mL at any time post-vaccination by GP-ELISA and over 80.0% of participants met seroresponse criteria defined as a  $\geq 4$  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 <sup>†</sup>	Protocol 011 <sup>†</sup>	Protocol 012 <sup>‡</sup>	Protocol 016 <sup>†</sup>	Protocol 018 <sup>†</sup>
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 <sup>§</sup>	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 titer

<sup>§</sup>Protocol 011 from Month 9-12

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

<sup>‡</sup>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 <sup>†</sup>	Protocol 011 <sup>†</sup>	Protocol 012 <sup>‡</sup>	Protocol 016 <sup>†</sup>	Protocol 018 <sup>†</sup>
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 <sup>§</sup>	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

## Product information for human medicinal products

### Paediatrics

#### 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  $\geq 2$ -fold increase from baseline and  $\geq 200$  EU/mL at any time post-vaccination by GP ELISA and 95.8% of participants met seroresponse criteria defined as a  $\geq 4$ -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]
<b>1 to &lt;3 Years</b>	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]
<b>3 to &lt;12 Years</b>	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]
<b>12 to 17 Years</b>	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]
<b>1 to &lt;3 Years</b>	17.5 (39) [<0, <0]	321.0 (33) [231.1, 445.7]	494.7 (32) [386.5, 633.3]

## Product information for human medicinal products

<b>3 to &lt;12 Years</b>	17.9 (134) [16.9, 18.8]	280.4 (114) [241.3, 325.7]	312.7 (88) [271.0, 360.8]
<b>12 to 17 Years</b>	17.5 (111) [17.4, 17.6]	273.3 (119) [237.5, 314.6]	251.7 (85) [215.7, 293.7]
<p>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.</p> <p>n = Number of participants contributing to the analysis.</p> <p>CI = Confidence interval; GMT = Geometric mean titre; PRNT = Plaque Reduction Neutralisation Test</p> <p>Protocol 016 used gamma irradiation of specimens to reduce risk of wild-type Ebola virus infection of laboratory workers.</p>			

### *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.

### **Pharmacokinetics**

#### *Absorption*

Not applicable

#### *Distribution*

Not applicable

#### *Metabolism*

Not applicable

#### *Elimination*

Not applicable

Pharmacokinetic studies and human biodistribution studies have not been performed.

### **Preclinical 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 «Pregnancy, lactation»).

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 «Dosage/Administration»). 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 «Warnings and precautions» and «Other information, Instructions for handling» for further information.

**Other information*****Incompatibilities***

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

***Shelf life***

Do not use this medicine after the expiry date ("EXP") stated on the container.

***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 until use. At

## Product information for human medicinal products

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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 (up to 14 days after removal from the freezer). Once thawed, the vaccine cannot be re-frozen.

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

Keep out of the reach of children.

### *Instructions for handling*

- The vaccine is stored frozen at  $-80^{\circ}\text{C}$  to  $-60^{\circ}\text{C}$  and should be removed from the freezer before administration and thawed completely 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 1 mL dose 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 accordance with local requirements 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.

### **Authorisation number**

68358 (Swissmedic)

### **Packs**

Pack size: carton box with 10 vials.

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

### **Marketing authorisation holder**

MSD Merck Sharp & Dohme AG

Lucerne

### **Date of revision of the text**

July 2024

