swissmedic

Date: 16 September 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Ervebo

International non-proprietary name: Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP, live).

Pharmaceutical form: solution for injection

Dosage strength(s): Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP live, attenuated) ≥72 million pfu

Route(s) of administration: intramuscular (IM)

Marketing authorisation holder: MSD Merck Sharp & Dohme AG

Marketing authorisation no.: 68358

Decision and decision date: approved on 10.11.2021

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

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
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
GP	Glycoprotein
HPLC	High-performance liquid chromatography
IC/EC_{50}	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
Pfu	Plaque-forming units
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)

New active substance status
The applicant requested new active substance status for Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP, live) in the above-mentioned medicinal product.

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 18 years 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 18 years 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 18 years of age or older: 1 dose (1 mL). One dose (1 mL) contains Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP live, attenuated) ≥72 million pfu

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	21 January 2021
Formal control completed	18 February 2021
Preliminary decision	18 June 2021
Response to preliminary decision	16 August 2021
Final decision	10 November 2021
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 (EMA/606159/2019, Procedure No. EMEA/H/C/004554/0000, first published: 12.12.2019), issued by the EMA.

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA The SwissPAR relating to quality aspects refers to the publicly available assessment report Ervebo (EMA/606159/2019, Procedure No. EMEA/H/C/004554/0000, first published: 12.12.2019), issued by the EMA.

4 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 (EMA/606159/2019, Procedure No. EMEA/H/C/004554/0000, first published: 12.12.2019), issued by the EMA.

5 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 (EMA/606159/2019, Procedure No. EMEA/H/C/004554/0000, first published: 12.12.2019), issued by the EMA.

6 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.

7 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).

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.

Placeholder for text approval stamp

▼ 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[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

Indications/Uses

Ervebo is indicated for active immunization of individuals 18 years 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 18 years of age or older: one dose (1 mL) (see section «Properties/Effects»).
The need for a booster dose has not been established.

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 safety, immunogenicity and efficacy of Ervebo in children aged 1 to 17 years have not yet 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 has been evaluated in the period ≥10 to ≤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. Vaccine virus RNA has been detected by PCR in the plasma of most of the adult subjects. Vaccine virus RNA was mainly detected from Day 1 to Day 7. Shedding of vaccine virus has been detected by PCR in urine or saliva in 19 out of 299 adult subjects and in skin vesicles in 4 out of 10 adult subjects. The vaccine virus RNA was detected in a skin vesicle at 12 days post-vaccination in one of the four subjects.

Viral shedding was observed more frequently in children and adolescents (28/39) compared to adults.

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

- Immunocompromised individuals and individuals receiving immunosuppressive therapy (see section above),
- Pregnant or breast-feeding women (see section «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».

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 subjects 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 infection.
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

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

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

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

Tabulated list of adverse reactions

Frequencies are reported as:

Very common (≥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.

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

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

[§]See description of selected adverse reactions.

Description of selected adverse reactions

Arthralgia and arthritis

Arthralgia was generally reported in the first few days following vaccination, was mild to moderate in intensity, and resolved within one week after onset. Arthritis (arthritis, joint effusion, joint swelling, osteoarthritis, monoarthritis or polyarthritis) was generally reported within the first few weeks following vaccination. In clinical trials with reports of arthritis, the median onsets were between 10 and 12 days

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

Rash

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

Transient decrease in white blood cells

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

Paediatric population

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

The safety profile of Ervebo in children and adolescents 6 to17 years of age was generally similar to that observed in adults.

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 ElViS portal (Electronic Vigilance System). You can obtain information about this at 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 (rVSVΔG-ZEBOV-GP). Immunisation of subjects with the vaccine results in an immune response and protection from Zaire Ebola Virus Disease (EVD). The relative contributions of innate, humoral and cell-mediated immunity to protection from Zaire Ebola virus are unknown.

Pharmacodynamics

Not applicable.

Clinical immunogenicity and efficacy

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

Clinical efficacy

Clinical efficacy of Ervebo was assessed in Protocol 010.

Protocol 010 (Ring vaccination study) was a Phase 3 open-label cluster-randomised trial of ring vaccination (vaccinating contacts and contacts of contacts [CCCs] of index Ebola cases) which evaluated efficacy and safety of Ervebo in Guinea. In this trial, 9,096 subjects ≥18 years of age who were considered CCCs of an index case with laboratory-confirmed EVD were randomised to immediate (4,539 subjects in 51 clusters) or 21 days delayed (4,557 subjects in 47 clusters) vaccination with Ervebo. Of those 9,096 subjects, 4,160 received Ervebo (2,119 subjects were vaccinated in the immediate arm and 2,041 subjects were vaccinated in the delayed arm). The median age of consenting CCCs was 35 years old. The final primary analysis included 2,108 subjects (51 clusters) vaccinated in the immediate arm and 1,429 subjects (46 clusters) eligible and consented on Day 0 in the delayed arm.

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

Clinical immunogenicity

No immune correlates of protection have been defined.

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

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

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

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

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

As shown in Tables 2 and 3, the geometric mean titers (GMT) of GP-ELISA and PRNT increased from pre-vaccination to post-vaccination. Over 93.8% of vaccine recipients met seroresponse criteria defined as a ≥2-fold increase from baseline and ≥200 EU/mL at any time post-vaccination by GP-ELISA and over 80.4% of subjects met seroresponse criteria defined as a ≥4 fold increase from baseline at any time post-vaccination by PRNT. Over 80.1% of subjects continued to meet the seroresponse criteria for GP-ELISA and over 63.5% of vaccine recipients continued to meet seroresponse criteria for PRNT at 12 months. The clinical relevance of the immunogenicity data is currently not known.

Immunogenicity data were obtained in Protocol 009 in Liberia, Protocol 011 in Sierra Leone, Protocol 012 in the United States, Canada, and Europe, and Protocol 018 in Guinea. Gamma irradiation of specimens (from regions involved in Ebola outbreaks) was performed to reduce risk of wild-type Ebola virus infection of laboratory workers, but increased pre-vaccination GP-ELISA immune responses by

approximately 20% and decreased post-vaccination GP-ELISA and PRNT immune responses by approximately 20%. Gamma irradiation, baseline seropositivity and other factors result in a higher immune response in Protocol 012.

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

Trial	Baseline GMT (n) [95% CI]	Month 1 GMT (n) [95% CI]	Month 6 GMT (n) [95% CI]	Month 12* GMT (n) [95% CI]	Month 24 GMT (n) [95% CI]
Protocol 009§	117.9 (464) [107.9, 128.7]	994.7 (475) [915.0, 1,081.3]	712.2 (477) [659.4, 769.3]	661.4 (475) [613.2, 713.4]	NA
Protocol 011§	92.7 (503) [85.3, 100.9]	964.3 (443) [878.7, 1,058.3]	751.8 (383) [690.6, 818.4]	760.8 (396) [697.6, 829.8]	NA
Protocol 012					
Combined Consistency Lots Group	< 36.11 (696) [<36.11, <36.11]	1,262.0 (696) [1,168.9, 1,362.6]	1,113.4 (664) [1,029.5, 1,204.0]	1,078.4 (327) [960.6, 1,210.7]	920.3 (303) [820.4, 1,032.3]
High Dose Group	< 36.11 (219) [<36.11, <36.11]	1,291.9 (219) [1,126.9, 1,481.2]	1,189.5 (215) [1,036.7, 1,364.9]	1,135.5 (116) [934.8, 1,379.3]	1,009.1 (105) [830.0, 1,226.7]
Placebo Group	< 36.11 (124) [<36.11, <36.11]	< 36.11 (124) [<36.11, <36.11]	< 36.11 (123) [<36.11, <36.11]	< 36.11 (65) [<36.11, <36.11]	< 36.11 (65) [<36.11, <36.11]
Protocol 018§	78.3 (1,123) [74.7, 82.0]	1,106.5 (1,023) [1,053.4, 1,162.2]	1,008.8 (75) [849.8, 1,197.6]	NA	NA

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

The Per-Protocol Immunogenicity Population was the primary population for the immunogenicity analyses in Protocol 012 and includes all subjects who were compliant with the protocol, received vaccination, were seronegative at Day 1, and had a serum sample at one or more timepoints collected within an acceptable day range.

n = Number of subjects contributing to the analysis.

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

*Protocol 011 from Month 9-12

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

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

Trial	Baseline GMT (n) [95% CI]	Month 1 GMT (n) [95% CI]	Month 6 GMT (n) [95% CI]	Month 12* GMT (n) [95% CI]	Month 24 GMT (n) [95% CI]
Protocol 009§	< 35 (428) [<35, <35]	116.8 (477) [106.0, 128.8]	76.8 (477) [69.9, 84.4]	100.4 (476) [91.4, 110.3]	NA
Protocol 011§	< 35 (438) [<35, <35]	116.0 (437) [105.7, 127.4]	95.3 (382) [86.3, 105.3]	119.9 (396) [107.9, 133.2]	NA
Protocol 012					
Combined Consistency Lots Group	< 35 (696) [<35, <35]	202.1 (696) [187.9, 217.4]	266.5 (664) [247.4, 287.0]	271.4 (327) [243.4, 302.7]	267.6 (302) [239.4, 299.2]
High Dose Group	< 35 (219) [<35, <35]	236.1 (219) [207.4, 268.8]	302.1 (215) [265.2, 344.1]	323.7 (116) [269.5, 388.8]	342.5 (105) [283.4, 414.0]
Placebo Group	< 35 (124) [<35, <35]	< 35 (123) [<35, <35]	< 35 (123) [<35, <35]	< 35 (65) [<35, <35]	< 35 (65) [<35, <35]

Protocol 018[§]	< 35 (1,107) [<35, <35]	160.0 (1,024) [151.6, 168.9]	117.0 (75) [96.0, 142.6]	NA	NA

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

The Per-Protocol Immunogenicity Population was the primary population for the immunogenicity analyses in Protocol 012 and includes all subjects who were compliant with the protocol, received vaccination, were seronegative at Day 1, and had a serum sample at one or more timepoints collected within an acceptable day range.

n = Number of subjects contributing to the analysis.

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

*Protocol 011 from Month 9-12

[§]Protocols 009, 011 and 018 used gamma irradiation of specimens to reduce risk of wild-type Ebola virus infection of laboratory workers

Paediatrics

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

Swissmedic has acknowledged an EMA exemption for this medicinal product from the requirement to submit results on studies in all paediatric age groups in the prevention of Ebola disease.

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 limited shedding in adults, the results of a toxicity study in non-human primates, and lack of horizontal transmission in pigs, the overall risk of Ervebo to human health and the environment is considered negligible. However, as a precaution, vaccinees should attempt to avoid exposure of livestock to blood and bodily fluids for at least 6 weeks following vaccination to avoid the theoretical risk of spread of the vaccine virus. People who develop vesicular rash after receiving the vaccine should cover the vesicles until they heal. Cover the vaccination site or any vesicles with an adequate bandage (e.g. any adhesive bandage or gauze and tape) that provides a physical barrier to protect against direct contact with vesicle fluid (see section «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 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°C to -60°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

November 2021

CCDS-V920-I-072020-OMA/RCN000015592-CH