

## **Environmental Risk Assessment for V920 Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP, live attenuated)**

Belgium Biosafety procedure

Public information document and non-confidential ERA.

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## GLOSSARY

Abbreviation/Acronym	Definition	Abbreviation/Acronym	Definition
EBOV	Ebolavirus	IM	Intramuscular
EMA	European Medicines Agency	MSD	Merck Sharp & Dohme Corp.
ERA	Environmental Risk Assessment	NHP	Non-human primates
EU	European Union	rVSV	Recombinant Vesicular Stomatitis Virus
EVD	Ebola Virus Disease	rVSVΔG-ZEBOV-GP	Recombinant Vesicular Stomatitis Virus with Envelope Glycoprotein replaced by Zaire ebolavirus (Kikwit Strain) Glycoprotein (V920)
GMO	Genetically Modified Organism	VSV	Vesicular Stomatitis Virus
GP	Glycoprotein	ZEBOV	Zaire ebolavirus

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## **EXECUTIVE SUMMARY**

V920 (also known as rVSVΔG-ZEBOV-GP, live attenuated) is a vaccine candidate for protection against Ebola Virus Disease (EVD) caused by Zaire Ebola virus that it currently is under regulatory review by the European Medicines Agency (EMA). V920 is a recombinant vesicular stomatitis virus (rVSV) in which the gene encoding for the VSV glycoprotein G has been deleted from its RNA and replaced with the Zaire Ebola virus (ZEBOV) glycoprotein (GP). The vaccine is genetically engineered, replication-competent, attenuated live virus that induces immune responses after a single dose.

Eight Phase 1/1b studies have been completed in North America (U.S. and Canada), Europe (Switzerland and Germany), and countries in Africa (Gabon and Kenya) to evaluate the immunogenicity and safety of V920 administered as pre-exposure prophylaxis. Additionally, four late phase studies have been completed in Sierra Leone, Liberia, Guinea, U.S., Canada and Spain, including one study which demonstrated efficacy for V920 in preventing disease due to Zaire ebolavirus in an area of transmission.

An Environmental Risk Assessment has been conducted in accordance with Directive 2001/18/EC in order to evaluate potential adverse effects and negative consequences for people other than the vaccinated persons and the environment at large. This assessment resulted in the conclusion that the risk of the intended use of V920 as a vaccine in Europe for people and the environment is estimated to be negligible.

Similar to other live viral vaccines, vaccinated persons should not donate blood within 1 month after vaccination. Shedding of virus in adult secretions or urine is infrequent, at low levels, and appears to pose minimal, if any, risk of transmission to other persons. Vaccine recipients should attempt to avoid close association with and exposure of high-risk individuals (i.e. immunocompromised individuals, pregnant or breastfeeding women, and children less than 1 year of age) to blood and bodily following vaccination. Individuals who develop vesicular rash after receiving the vaccine should cover the vesicles until they heal.

The risk of infection or disease in livestock is a theoretical concern due to the nature of the parental VSV virus. Transmission from humans to animals is unlikely, though, due to the low levels of virus shedding by vaccinated persons. As an extra precaution, vaccinated individuals should attempt to avoid exposure of livestock to blood and bodily fluids following vaccination.

Transmission of the vaccine virus from vaccinees to other humans and to the environment is estimated to be a negligible risk. If transmitted, the vaccine virus would retain its attenuated phenotype. V920 has no selective advantage for replication, virulence or pathogenicity. Gene

transfer from V920 to other species is not expected. Finally, as V920 does not cause long-lasting viremia in humans or animals, the probability of co-infection is further minimized. Thus, the generation of new chimeric viruses affecting new animal species is only a low probability theoretical possibility.

In conclusion, risk to humans and the environment from exposure to the vaccine is estimated to be negligible.

## **1. INTRODUCTION**

### **1.1. General overview on the product**

V920 (also known as rVSVΔG-ZEBOV-GP, live attenuated) is a vaccine candidate for protection against Ebola Virus Disease (EVD) caused by Zaire Ebola virus that is currently being investigated in multiple clinical trials [1]. The V920 vaccine candidate is a recombinant vesicular stomatitis virus (rVSV) which has the gene encoding for the VSV glycoprotein G deleted from its RNA and replaced with the Zaire Ebola virus (ZEBOV) glycoprotein (GP). The vaccine is a genetically engineered, replication-competent, attenuated live vaccine that induces immune responses after a single dose. The vaccine virus is grown in Vero cells to produce the Bulk Drug Substance, the vaccine Drug Product is a solution for injection manufactured by aseptic addition of the Bulk Drug Substance. The vaccine is manufactured by Merck Sharp & Dohme B. V.

Immunogenicity as well as pre- and post-exposure prophylactic efficacy of V920 has been demonstrated following a single intramuscular (IM) injection in multiple nonclinical studies in rodent species [2] and non-human primates (NHP) [3] [4].

A preventive vaccine could be used to protect individuals at high risk in advance of exposure and could be used for outbreak control at a population level to interrupt transmission. Since V920 elicits rapid immunity after a single dose, it has important potential for use in this context.

Eight Phase 1/1b studies have been completed in North America (U.S. and Canada), Europe (Switzerland and Germany), and countries in Africa (Gabon and Kenya) to evaluate the immunogenicity and safety of V920 administered as pre-exposure prophylaxis. Additionally, four late phase studies have been completed in Sierra Leone, Liberia, Guinea, U.S., Canada and Spain, including a study which demonstrated efficacy for V920 in preventing disease due to ZEBOV in an area of ongoing transmission.

### **1.2. V920 Regulatory and legal background**

According to European regulatory framework for live recombinant viral vectored vaccines of 24 June 2010, EMA/CHMP/VWP/141697/2009, legal requirements for GMOs apply and including an Environmental Risk Assessment, as outlined in Regulation 726/2004 and in accordance with Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of GMOs (Annex II, III and IV) and any guidance documents published by the Commission in connection with the implementation of this Directive.

This document provides non-confidential information related to the risks to medical personnel, persons in contact with the treated Individuals who may potentially be exposed to the Vaccine candidate.

### **1.3. General information on V920 according to Annex IV of Directive 2001/18/EC**

#### **1.3.1. Description of intended use of V920**

The Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP, live attenuated) is indicated for active immunization of at risk individuals 18 years and older to protect against Ebola Virus Disease (EVD) caused by Zaire Ebola virus.

#### **1.3.2. Justification of intended use of V920**

There are no specific medical interventions licensed to treat Ebola hemorrhagic fever globally and there are no licensed vaccines in the European Union (EU).

The virus is classified as a Category A priority pathogen, the highest level of risk to national security and public health. Thus, there is a high unmet medical need for a vaccine for those living and working in areas at risk for Ebola epidemics.

Treatment of Ebola hemorrhagic fever is mainly supportive, involving fluid and electrolyte replenishment and pain reduction.

Immunization with V920 has been shown to be generally well-tolerated in healthy, nonpregnant adults. The vaccine will be contraindicated in individuals with hypersensitivity to the active substances or to any of the excipients.

Administration of V920 is planned in controlled situations such as hospitals or vaccination centers. Likely environments for dispensing and use will include the field/community (e.g. outbreak containment situations), or within select designated inpatient environments (e.g. travel clinic, Ebola treatment facility, etc.) based on relevant policy and program requirements (e.g. first responders, healthcare workers, lab scientists, travelers, etc.).

Only trained medical personnel will handle and administer V920 to individuals.

### **1.4. Determination of the overall risk of licensing of V920**

The overall risk of V920 to human health and the environment is estimated to be negligible based on an evaluation of the magnitude of potential adverse effects and likelihood of occurrence.

Management strategies demonstrate that exposure of V920 to people and animals can be prevented altogether. Administration of the vaccine would take place under controlled conditions in order to prevent release into the environment by accident.

Furthermore, as demonstrated by clinical data, shedding from vaccinated people is very limited and makes it highly unlikely that V920 reaches the environment at large. Even in a worst case, if there was transmission from a vaccinated individual, the data suggest minimal or no untoward effects in the recipient organisms and no further spread.

## 2. DISCUSSION AND CONCLUSION

The V920 vaccine has been successfully administered to rodents (mice, rats, and hamsters), non-human primates, pigs, arthropods, and humans. Transmission of the vaccine virus from vaccinees to other humans and to the environment appears to represent a negligible risk.

Persons vaccinated with V920 typically had low levels of virus in their blood for up to 1 week after vaccination, and all subjects assessed to date have cleared the virus from their blood by Day 28 post-vaccination. Similar to other live viral vaccines, V920 vaccinated persons should not donate blood at least 1 month after vaccination.

Vesicular lesions of the skin appearing in the first 2 weeks after vaccination are rare, but are a potential source of virus infection; care should be taken to avoid contact spread from such lesions to others, including animals, by covering the vesicles until healing occurs.

Shedding of virus in adults, as measured to date in saliva or urine, is infrequent, at low levels, and appears to pose minimal, if any, risk of transmission to other persons. Therefore, vaccine recipients should attempt to avoid close association with and exposure of high-risk individuals to blood and bodily fluids following vaccination.

Transmission from humans to animals is unlikely due to the minimum levels of virus shedding by human vaccinees and management strategies to prevent direct contact of vaccinated individuals with animals during the period of potential shedding.

In conclusion, risk to humans and the environment from exposure to the vaccine is estimated to be negligible. However, risk management measures as described above should be implemented to limit exposure to V920 to the full extent possible.

## List of references

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