Public information

Wageningen Bioveterinary Research

A Phase 1, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerance, and immunogenicity of a live-attenuated Rift Valley fever vaccine (hRVFV-4s) in healthy volunteers

European notification number

Eudra CT: 2020-003362-39

The introduction of genetically modified organisms (GMOs) into the environment is strictly regulated at European level by Directive 2001/18/EC of 12 March 2001 replacing Directive 90/220/EEG and at the Belgian level by a Royal Decree of 19 February 2020 “regulating the deliberate release into the environment as well as the placing on the market of genetically modified organisms or of products containing them” to replace the Royal Decree of 21 February 2005. To ensure the safe use of GMOs, the legal texts stipulate that the release of GMOs for experimental purposes is prohibited without prior written permission from the competent minister. Admission or denial is based on a careful evaluation of the biosafety of the planned release, which is carried out by the Biosafety Advisory Council. This advisory board is composed of various scientific committees that groups independent experts from Belgian universities and government institutions. In order to obtain the required authorization from the competent minister, Wageningen Bioveterinary Research has submitted an application file to the competent authority. Based on the advice of the Biosafety Council, the competent minister can grant permission to Wageningen Bioveterinary Research to perform the experiments with a candidate vaccination treatment as described in the application B_BE_21_BVW2. The introduction is foreseen at the Center for Vaccinology (CEVAC), University Hospital Ghent, Corneel Heymanslaan 10, 9000 Ghent, Belgium.

The trial is expected to start on November 8, 2021 and be completed on October 24, 2022.

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General information

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Introduction

In this clinical trial a candidate vaccine is being tested against the Rift Valley fever virus (RVFV). The vaccine, called hRVFV-4s, is injected into the muscle once.

Description of the GMO

The hRVFV-4s vaccine is a so-called live-attenuated vaccine. This means that the vaccine is based on a weakened form of the virus against which the vaccine must protect: the Rift Valley fever virus (RVFV). RVFV is a virus that is spread by mosquitoes to animals and humans. The virus is currently found in Africa and the Arabian Peninsula and there are indications that the habitat of the virus is expanding.
The virus mainly affects domestic ruminants (sheep, goats, cattle), resulting in the death of newborn animals and abortion during pregnancy, especially in sheep. Infection of humans generally manifest with flu-like symptoms, but up to 10% of patients experience retinal damage that can lead to temporary or permanent blindness. Two percent of infected individuals develop even more serious complications, including encephalitis and hemorrhagic fever. The latter syndrome in particular has a high mortality rate. No vaccine for use in humans is currently available.

The live-attenuated hRVFV-4s vaccine virus is still capable of infecting animal and human cells, but does not cause disease in animal models. Because the vaccine is indistinguishable from the pathogenic virus by the immune system, a highly effective protective “immune response” is elicited. The virus has been weakened by genetic modification. In this particular case, some of the genetic material of the virus has been removed and another portion of the genetic material has been cut into two pieces. The vaccine is therefore considered a **G**enetically **M**odified **O**rganism (GMO).

Nature and purpose of the intended trial

The study is a "First-in-Human" (FIH; or "a study performed in human for the first time") clinical trial with the hRVFV-4s vaccine. The study will be conducted with a total of 75 healthy subjects aged 18 to 45 years old.

The healthy volunteers are assigned to one of three test groups, each consisting of 25 subjects. In each group, the vaccine is administered to 20 subjects, with one group receiving a low dose, one group receiving a medium dose, and one group receiving a high dose. From each group of 25 persons, 5 persons will be administered a placebo.

The vaccine is designed to induce a strong and long-lasting immune response characterized by antibody responses and cellular immune responses (T cells).

The main purpose of this trial is to determine the safety of the vaccine.

Participants will receive their vaccination and will be assessed in the hospital. If the injection does not cause immediate (within 1 hour) symptoms and the participant does not feel ill, he/she does not need to stay in hospital and can continue normal work- and family life.

On day 28 after vaccination of the first test group (low dose vaccine), the safety of the vaccine is assessed by a Data Safety Monitoring Board (DSMB). If the DSMB considers the vaccine to be sufficiently safe based on the data available on day 28 after vaccination, vaccination of the second test group (medium dose vaccine) will be started. Vaccination of the third test group (high dose vaccine) will again follow after approval of the DSMB. Each test group is followed up for 180 days.

Research & Development activities

Previous development activities

This is the first clinical study with this vaccine in humans. Tests with animal models have already been carried out in advance to:

- Demonstrate the efficacy of the vaccine: Previous studies conducted with mice, rats, lambs, pregnant ewes and nonhuman primates showed that vaccination with the vaccine elicits protective antibodies and the experiments with mice and lambs showed complete protection from the pathogenic virus after a single vaccination.
- Demonstrate the safety of the vaccine: A study with mice with a weakened immune system, a study with pregnant ewes and a study with non-human primates showed that the vaccine is completely safe for animal species that are highly susceptible to the pathogenic virus. In these studies, a dose was administered corresponding with (more than) the highest dose that will be administered to humans in the clinical study.

Future activities

When the results of this human clinical trial show that vaccination is completely safe and induces protective antibodies, the study will be followed by a larger study in Kenya, where RVFV is presently circulating. Demonstrating the safety and efficacy of the vaccine in an African population is important, as this population is genetically different from the European population. When sufficient data have been collected, these will be shared with the competent authorities in different countries. These authorities will study the data thoroughly and, if appropriate safety and efficacy is endorsed, they will authorize the vaccine to be made available to people at risk of exposure to RVFV.

Benefits

RVF is a disease that mainly affects domesticated ruminants. Farmers, veterinarians and people working in the slaughter line are most at risk of infection from contact with contaminated tissues and bodily fluids, especially blood. In most cases human infection results in flu-like symptoms without serious consequences. However, up to 10% of infected individuals develop retinal damage, which may result in temporary or permanent blindness. Up to 2% of infected people develop a more serious clinical presentation, which can manifest as encephalitis (inflammation of the brain) or hemorrhagic fever. The latter syndrome, in particular, can result in death. There is currently no vaccine or treatment available.

Risks

As the vaccine is a GMO, a detailed environmental risk assessment was performed in addition to the standard risk assessment for clinical studies. The main considerations are:
(i) The risk of the vaccine virus reverting to virulence and causing disease. The pathogenic virus has the ability to counteract the host's defenses. The vaccine has been genetically modified in such a way that this ability has been lost. To further weaken the virus, some of the virus' genetic material has been split into two pieces. This makes it more difficult for the virus to make new virus particles, giving the host even more opportunity to develop an immune response. Both weakening mutations were shown to be stably maintained.
(ii) The risk that the vaccine could be transferable to other people. Based on the arguments below, this risk is considered to be negligible.

Containment, control and follow-up measures

Control of GMO and gene distribution

The vaccine is injected into the muscle, which makes the occurrence of significant leakage from the injection site unlikely. The injection site will also be cleaned and covered with a dressing. Studies with animal models have shown that the virus does not migrate from the injection site to other parts of the body. Furthermore, it has been shown in animal models that the virus does not replicate detectably after administration. The vaccine virus is therefore unlikely to persist in humans. Animal studies have also shown that the vaccine virus is not excreted in urine and faeces, and is not present in the testes. However, even if the vaccine virus comes in contact with an individual who is not part of the study, it is not possible for the vaccine virus to spread further into the environment.

Genetic stability of the GMO

The vaccine virus does not replicate, at least not to detectable levels, in animal models and is therefore not expected to replicate in humans. This makes the risk of genetic changes very small. In addition, it has been shown that the genetic modifications have rendered the virus non-

pathogenic, that the modifications are stably maintained, and that the modifications cannot be repaired by the virus. The genetic material of the vaccine also cannot be incorporated into the cells of vaccinated persons.

Destruction of the GMO-containing material

The intended study is a deliberate introduction of the hRVFV-4s vaccine into a clinical trial. The vaccine is used for this study only and use of this material for any other purpose is prohibited. Unused vaccine will be returned to the manufacturer or destroyed. All waste material generated from the use of the vaccine in the clinical trial will be destroyed by companies specialized in destroying GMO waste. This waste may include empty bottles, syringes and needles, as well as masks, plastic aprons and disposable gloves used during the administration of the vaccine.
The hospitals have high-risk medical waste containers to collect these materials before they are collected for disposal:
• Waste bins for: cardboard, bandages, masks, aprons, gloves
• Waste bins for sharps: bottles, syringes, needles, dilution kits
All these containers of hazardous medical waste are clearly labeled and collected at specific locations in the hospital before being disposed of.

Training requirements

All CEVAC employees involved in handling the vaccine will receive extensive training on how to properly handle GMO material and will follow written procedures, including the use of personal protective equipment (PPE) such as masks, aprons, gloves and eye protection. The personnel who will receive/store the vaccine and be involved in preparing the vaccine dosage and giving the injections to the trial participants will be trained according to the Pharmaceutical Manual developed specifically for this trial.

Emergencies

Any accidental exposure to the vaccine will be reported according to hospital policy and handled as specified in the Pharmaceutical Manual and the procedures applicable in the hospital. The vaccine virus can be inactivated with appropriate disinfectants. These disinfectants will be available in the hospital and can be used to clean up spills.
• needle stick injuries: thoroughly clean the area with disinfectants;
• ingestion/ingestion: rinse mouth thoroughly with clean water, report event to relevant hospital doctor;
• inhalation: report the incident to the relevant doctor in the hospital;
• skin/eye exposure: report the event to the relevant hospital doctor;
• spillage: Trained personnel equipped with PPE will clean the area using disinfectant. All waste will be disposed of in the relevant GMO biohazard containers.

Other containment, control and follow-up measures

Responsibility of the notifier

The authorization granted by the competent Minister to the notifier states that the notifier bears full civil liability for all damage caused to humans, animals and the environment as a result of this deliberate release.

Inspection by the authorities

The authorized inspectors shall verify that the clinical study is conducted in accordance with the conditions specified in the authorization and identify any violations of the authorization granted. Sanctions will be imposed when mismanagement or fraud is established.

Activity report

Once the clinical trial is concluded, the notifier shall prepare an activity report and submit it to the competent authorities. This activity report contains at least the following information:
• The place and period of deliberate release,
• The exact nature of the actually released GMOs,
• The objective(s) of this clinical study,
• The measures taken to avoid unwanted release of transgenic material,
• If applicable, the measures taken to protect the subjects during the administration of the vaccine,
• The measures taken to protect personnel handling the GMO-containing material,
• The results of the clinical study with regard to the safety of the GMO,
• An overview of the controls on the possible excretion of the vaccine by the subjects.

Word list

Encephalitis	Inflammation of the brain
Faeces	Stool
GMO – Genetically Modified Organism	Any organism whose genetic material has been altered using genetic modification techniques.
Hemorrhagic fever	A clinical presentation accompanied by fever and severe internal bleeding.
Immune response	The body's response to a "foreign" entity, such as an infectious virus.

T-cell	A type of white blood cell that helps regulate the immune response and kills infected cells.
Testes	Testicles
Virus	A small infectious organism that can enter the cells of the body.

Contact details

Please contact us at the address below if you have any comments regarding this public record or our activities, or if you would like to receive additional information about this deliberate release.

You can also consult a summary of this notification (Summary Notification Information Format or SNIF) on the website of the Joint Research Center of the European Commission (http://gmoinfo.jrc.ec.europa.eu/). You can also submit your comments to the Commission via this website.

Notifier:

Wageningen Bioveterinary Research
Houtribweg 39
8221 RA
Lelystad
The Netherlands

Contact: +31 320-238800