INFORMATION FOR THE PUBLIC

AstriVax NV

LAV-YF17D/RabG

LAV-YF17D/RabG will be assessed in Part 2 of clinical study AVX12A-001_AVX48A-001 entitled: *A Phase I, randomized, double-blind, multi-centre, placebo-controlled, dose-escalation study to evaluate the safety, reactogenicity and immunogenicity of AstriVax' investigational vaccine for the prevention of yellow fever (AVX70120), and of AstriVax' investigational vaccine for the prevention of rabies (AVX70481), in healthy adults aged 18 to 40 years*

Deliberate Release Reference Number
B/BE/23/BVW3

The release of genetically modified organisms (GMOs) in the environment is strictly regulated at European level by Directive 2001/18/EC and at Belgian level by the Royal Decree of 21 February 2005. To ensure safe use of GMOs, the provisions of the Royal Decree of 21 February 2005 stipulate that the release of GMOs for experimental aims is prohibited without prior consent from the competent Minister. The decision is based on a thorough evaluation of the biosafety of the planned release, which is conducted by the Biosafety Advisory Council, composed of different Scientific Committees grouping independent experts from Belgian universities and governmental institutes.

To acquire the necessary authorization from the competent Minister, AstriVax submitted an application dossier to the competent authority. On the basis of the advice of the Biosafety Council, the competent Minister could grant a permission to AstriVax to conduct Part 2 of the above-mentioned clinical study in which the genetically modified organism LAV-YF17D/RabG will be assessed, as stipulated in the application B/BE/23/BVW3.

The clinical study will take place at two hospitals in Flanders:

- Centre for Evaluation of Vaccination (CEV) / Vaccinopolis, Antwerp (Edegem)
- Centre of Vaccinology (CEVAC), Ghent

Part 2 of clinical study is expected to start in August 2024 and to be completed in December 2025.

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GENERAL INFORMATION

Goal of the Genetic Modification

The genetically modified organism (GMO) is called live attenuated virus (or 'LAV' in short)-YF17D/RabG. The goal of LAV-YF17D/RabG is to protect people against rabies.

The rabies virus is a very dangerous virus, and it can infect humans and animals, such as dogs, bats and foxes. Humans usually get infected when they are bitten by an infected animal. Once a person is infected, the rabies virus slowly travels to the brain of that person over the next weeks and even months. Once the virus gets to the brain, the person gets clinical symptoms that are not very specific at first (for instance fever and headache). However, as the brain gets more and more infected, the symptoms get worse and the person can become confused, anxious, paranoid, start hallucinating, show abnormal behaviour, or be unable to sleep. Once the clinical symptoms start, rabies disease is nearly always deadly. Less than 20 cases of human survival from clinical rabies are known. There are already vaccines available that prevent rabies, however, many people do not have access to them. That is why more vaccines are needed.

Description of the Genetically Modified Organism (LAV-YF17D/RabG)

LAV-YF17D/RabG was made by adding the genetic code for the surface protein of the rabies virus (RabG) in that of the yellow fever vaccine strain 17D (YF17D). YF17D particles are a weakened (or attenuated) form of the yellow fever virus. YF17D is used as the vaccine to protect people against yellow fever.

LAV-YF17D/RabG particles look and behave the same as the YF17D particles in the YF17D vaccine, but each LAV-YF17D/RabG particle has the genetic code of the RabG protein included. When the LAV-YF17D/RabG particles multiply in the body of a vaccinated person, new RabG proteins are made. The RabG protein is foreign to humans, and it will trigger the body's natural defense mechanism to make antibodies. These antibodies recognize and attach to RabG. In nature, the RabG protein is part of the rabies virus. The virus needs the protein to attach to and get into human cells. If the RabG protein is blocked, the rabies virus cannot get into the human cells and is not dangerous anymore. The antibodies against RabG that are made in response to LAV-YF17D/RabG will recognize the RabG protein also when it is part of the real rabies virus. That way, if the person gets infected with rabies virus later in life, the body's natural defense mechanism will already know RabG and can quickly attack and destroy the virus.

As described above, LAV-YF17D/RabG was made by adding the genetic code for RabG in that of the yellow fever YF17D vaccine. The YF17D vaccine is in use since 1938 and more than 800 million people have been vaccinated with it. Because of this, a lot is known about YF17D, including that:

- The YF17D particles multiply in the body of a person who got the vaccine, and a few days after the vaccination, a low number of particles can be present in some of the bodily fluids (for instance the blood or the urine). Once the person's natural defense mechanism kicks in, and he / she starts making antibodies against the YF17D particles, the YF17D particles are destroyed and disappear from the body.
- The weakened YF17D particles cannot spread from one person to another like the real yellow fever virus can. The real yellow fever virus spreads from one person to another through the bite of infected mosquitoes that live in South and Central America or in Africa. The mosquitoes become infected when they bite a person who has yellow fever virus in his or her blood. While YF17D particles can be present in the blood of a vaccinated person, there are way too few particles for mosquitoes to become infected with YF17D. On top of that, even if mosquitoes would become infected with YF17D, it is so weakened that the mosquitoes cannot spread it to humans.
- The only way the YF17D particles could spread from one person to another, is if the other

person is in direct contact with the bodily fluids of the vaccinated person. This could for instance happen through a blood transfusion or an organ transplant, or possibly also if a vaccinated mother is breastfeeding. If a pregnant woman is vaccinated with the YF17D vaccine, it could also be possible that the YF17D particles spread to her unborn baby.
- The YF17D particles cannot survive for a long time outside the body.

Because the LAV-YF17D/RabG particles look and behave the same as the YF17D particles in the YF17D vaccine, all of this is also goes for the LAV-YF17D/RabG particles.

Description of the Vaccine (PLLAV-YF17D/RabG)

LAV-YF17D/RabG is not given as such to people. Instead, a DNA vaccine that has the genetic code for LAV-YF17D/RabG is given. The DNA vaccine is called plasmid-launched live attenuated virus (or 'PLLAV' in short)-YF17D/RabG. When PLLAV-YF17D/RabG is given to humans, the vaccine will go into the human cells. In the cells, the DNA will be used to make the LAV-YF17D/RabG particles. The LAV-YF17D/RabG particles will be released from the cells and infect and multiply in other cells.

The DNA vaccine itself, PLLAV-YF17D/RabG, cannot spread in the body. It is cleared away at the location where the vaccine is given.

RESEARCH / DEVELOPMENT ACTIVITIES

Previous Development Activities

Up to now, only testing in animals has been done. In animals, we saw that LAV-YF17D/RabG particles can trigger the animal's natural defense system to make antibodies against the RabG protein. We also saw that very low amount of the genetic material of LAV-YF17D/RabG particles was present for a short while in some of the organs and in the blood of some of the animals. Before the testing in humans will start, another study in animals will be done to make sure that there are no toxic effects.

Future Activities: Clinical Study

LAV-YF17D/RabG will be tested for the first time in humans in the second part of a clinical study called "*A Phase I, randomized, double-blind, multi-centre, placebo-controlled, dose-escalation study to evaluate the safety, reactogenicity and immunogenicity of AstriVax' investigational vaccine for the prevention of yellow fever (AVX70120), and of AstriVax' investigational vaccine for the prevention of rabies (AVX70481), in healthy adults aged 18 to 40 years."*

The main goal of the study is to make sure that PLLAV-YF17D/RabG DNA vaccine and the LAV-YF17D/RabG particles are safe in humans. For that reason, the first 12 people who join the study will get a very low dose of the vaccine. If there are no safety issues in these people, the next 24 people will get a higher dose. And if there are no safety issues in these people, the last 12 people will get the highest dose of the vaccine.

Apart from its safety, we will check if the LAV-YF17D/RabG particles can trigger the person's natural defense system to make antibodies and other immune cells that can attack the rabies virus. We will also check if we can find LAV-YF17D/RabG particles in the blood, the urine or the stool of people who got vaccinated with PLLAV-YF17D/RabG.

The people who take part in the study will be healthy and between 18 and 40 years old. After the vaccination, they will be followed up for 1 year. During this year, they will go to the clinic regularly for follow-up visits.

POTENTIAL BENEFITS

LAV-YF17D/RabG may protect people against rabies.

POTENTIAL RISKS

Potential Risks for Human Health Linked to the Deliberate Release

The LAV-YF17D/RabG particles cannot naturally spread from one person to another. The only way anyone could accidently get infected with LAV-YF17D/RabG particles is if:

- Personnel at the hospital that is doing the clinical study accidently self-administers the PLLAV-YF17D/RabG vaccine, for instance through a needle stick injury. Or if they are directly exposed to a blood, urine or stool sample that is taken from a person who takes part in the study, for instance if they spill a blood sample on a skin cut or graze.
- Someone gets a blood transfusion or an organ transplant from someone who takes part in the study.
- If a woman who takes part in the study is breastfeeding her child, or if she is pregnant.

Even if one of these situations would happen, it is still unlikely that the person would get infected with LAV-YF17D/RabG particles, because only a low number of LAV-YF17D/RabG particles will be present for a short period of time in some of the bodily fluids of some of the vaccinated persons. Or in the case of a needle stick injury, the dose of PLLAV-YF17D/RabG will be much lower than what will be given in the clinical study. On top of that, we will put measures in place to avoid these situations. The risk that someone will accidently get infected with LAV-YF17D/RabG particles is therefore low to negligible.

However, if someone were to get accidently infected with LAV-YF17D/RabG, the potential risks would be the same those for the people who are vaccinated with PLLAV-YF17D/RabG in the clinical study. These are:

- The risk of having side effects (for instance pain or redness at the place of the injection, or headache, feeling weak or unwell, muscle pain, fever, chills). Side effects could very rarely also be serious. The risk of having any side effect is low to moderate, while that of having serious side effects is low to negligible.
- A risk for the genetic material of the LAV-YF17D/RabG particles to slightly change (mutate) while it multiplies in the body, which make that the particles cause more side effects. This risk is low to negligible because we know that the genetic code of the existing YF17D vaccine is very stable.
- A theoretical risk that the genetic material of the LAV-YF17D/RabG particles could mix with that of a similar virus (for instance YF17D or the real yellow fever virus). This can only happen if both are present in the same cells of the same person. In this case a new (mixed) virus could be made. The risk of this is however negligible because not only is the appearance of a new (mixed) virus very unlikely in this type of viruses, it is also very unlikely for a person to have both viruses present. Indeed, the clinical study takes place in Belgium, where viruses like yellow fever are not present, and vaccination against this type of viruses is not routinely done.

If the body's natural defense system of the person who accidently gets infected with LAV-YF17D/RabG is weakened, or not fully developed yet (for infants), the type of risks would be the same. However, the chance for the risk to occur may be higher because their natural defense system cannot destroy the LAV-YF17D/RabG particles so quickly.

Potential Risks for the Environment Linked to the Deliberate Release

The LAV-YF17D/RabG particles cannot survive for a long time outside the body. The risk related to release of LAV-YF17D/RabG particles into the environment (for instance if the urine from a vaccinated person goes into the wastewater) is therefore negligible.

CONTAINMENT, CONTROL AND MONITORING MEASURES

Measures to Limit the Risks for Human Health

While it is very unlikely that LAV-YF17D/RabG particles will accidently spread to people who are not taking part in the clinical study, the following measures will be put in place to completely avoid this:

- All hospital personnel working on the study will be trained. They will wear a lab coat when they handle the PLLAV-YF17D/RabG vaccine, or samples (for instance blood samples) from people who take part in the clinical study.
- PLLAV-YF17D/RabG vaccine will be stored in vials that have a rubber stopper and a flip-off cap.
- All samples (for instance blood samples) from people in the clinical study will be stored in tubes that have a screw cap. If someone accidently spills a sample, the area will be thoroughly disinfected.
- All waste that may contain PLLAV-YF17D/RabG vaccine or LAV-YF17/RabG particles will be treated as hazardous medical waste.
- People who take part in the study cannot give blood or organs for 3 months after the vaccination. They cannot get pregnant until at least 2 months after the vaccination (this includes the partners of men who take part in the study). If a woman takes part in the study, she cannot be pregnant or breastfeeding.
- While the LAV-YF17D/RabG particles cannot naturally spread from one person to another, in order to avoid all risk to people with a weakened or unmature immune system, the people who take part in the study cannot live with, or be the caregiver of an immunocompromised person or an infant younger than 6 months of age.
- People who take part in the study cannot have a weakened immune system themselves. This is for their own safety, but it also limits the risk of spreading of LAV-YF17D/RabG particles. Indeed, as their body's natural defense mechanism is weakened, the particles would have more time to multiply before being destroyed.

Measures to Limit the Risks for the Environment

If a sample taken from people who take part in the clinical study is accidentally spilled, the surface will be thoroughly disinfected. No other measures will be put in place because there the risk related to release of LAV-YF17D/RabG into the environment is negligible.

Emergency Situations

If hospital personnel working on the clinical study accidently self-administers the PLLAV-YF17D/RabG vaccine, he / she will report this to the responsible person in the hospital.

If hospital personnel working on the clinical study accidently spill a sample from someone who takes part in the study, they will thoroughly disinfect the area.

GLOSSARY

Antibody. A protein in the blood that helps the body's natural defense mechanism by recognizing and attaching to specific foreign substances.

Clinical Study. A research study to test an intervention (for instance a medicine or a vaccine) in people.

DNA. Genetic material. DNA is made of molecules which provide the code for making proteins.

Genetic code. The order of the molecules in DNA defining the composition of the proteins.

Genetically modified organism. An organism (microbe, plant or animal) whose genetic code has

been changed using genetic engineering techniques.

Immune cells. The cells of the body's natural defense mechanism. Immune cells include antibodies but also other cells that help the antibodies to destroy foreign organism such as viruses.

Vaccine. Vaccines prepare the body's natural defense system to fight off organisms that can cause illness. They prevent the illness from being established in the vaccinated person. Vaccines introduce the body to foreign substances. As a result, the body's natural defense mechanism will start making antibodies and other immune cells against the foreign substance. That way, the body's natural defense mechanism will recognize the substance as a target for attack. In the future, if an organism that contains this substance enters the body, the body's natural defense mechanism already knows it and can quickly attack and destroy it.

Virus. A very small (not visible for the naked eye) organism, which can infect and multiply in the cells of other organisms such as animals or humans.

CONTACT

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