Information for the public

Short trial title: A trial to learn more about an experimental gene therapy called bidridistrogene xeboparvovec (SRP-9003) as a possible treatment for limb girdle muscular dystrophy 2E/R4

Full trial title: A Phase 3 multinational, open-label, systemic gene delivery study to evaluate the safety and efficacy of SRP-9003 in subjects with limb girdle muscular dystrophy 2E/R4

EU clinical trial number: 2022-503112-17-00

Brief description of the project

Limb girdle muscular dystrophies, or **LGMDs** for short, are a group of rare diseases that affect the muscles. LGMDs are caused by genetic mutations. These genetic mutations cause errors in the instructions our bodies have for making proteins that are important for muscle health. Without these proteins, people with LGMD have muscle loss and weakness that gets worse with time.

One type of LGMD is called LGMD Type 2E/R4, or **LGMD2E/R4** for short. People with LGMD2E/R4 have a genetic mutation that prevents them from making a protein called beta-sarcoglycan (or **beta-SG**, for short). People with LGMD2E/R4 usually start to show symptoms, such as difficulty running, jumping, and climbing stairs, before age 10. They typically lose the ability to walk without help in their teens. LGMD2E/R4 is also associated with early death. There is currently no treatment or cure for LGMD2E/R4.

Description of the genetic modified organism (GMO)

Bidridistrogene xeboparvovec (also known as **SRP-9003**) is an experimental **gene therapy**. Gene therapy is designed to treat the underlying cause of a genetic disease. Bidridistrogene xeboparvovec is designed to contain a corrected version of the mutated gene that causes LGMD2E/R4. It also includes a **vehicle** (also called a **vector**) that is intended to protect the corrected gene and deliver it to the cells where the non-working gene needs to be replaced.

The goal of treatment with bidridistrogene xeboparvovec is to replace the non-working gene with one that works, which may allow a person with LGMD2E/R4 to make beta-SG.

Primary objective of the research project: To learn about the effect of bidridistrogene xeboparvovec on the production of beta-SG in the muscles.

Approximately 15 participants with LGMD2E/R4 will receive bidridistrogene xeboparvovec worldwide, including 2 to 4 participants in Belgium.

What treatments will the participants get?

All of the participants will receive 1 dose of bidridistrogene xeboparvovec. Treatment takes approximately an hour and a half and will be given intravenously (through a needle in the vein). All participants will also take a type of medication called a steroid. Participants will take a steroid orally (by mouth), starting the day before treatment with bidridistrogene xeboparvovec and for at least 2 months after.

How long will participants be in the trial?

Participants will be in the trial for up to 66 months (about 5 ½ years). This includes 6 months before treatment and 5 years after treatment. In Belgium, the trial will start in May 2024 and end in January 2031.

Who can take part in this trial?

This trial will include people who are at least 4 years old and who have LGMD2E/R4 confirmed by genetic testing. This trial will not include people who have received gene therapy, stem cell transplants, or gene editing treatment. In addition, people with certain medical conditions may not be able to take part in the trial.

Where will this trial take place?

In Belgium, this trial will take place at these sites (locations):

Site 1	UZ Leuven Herestraat 49 3000 Leuven Belgium
Site 2	UZ Gent Corneel Heymanslaan 10 9000 Gent Belgium

There will be about 12 to 14 trial sites in this trial globally.

The nature, goal, and the potential advantages of the foreseen deliberate release

The goal of bidridistrogene xeboparvovec gene therapy is to increase production of beta-SG in the muscles. The hope is that this will slow the progression of muscle weakness that typically happens to people with LGMD2E/R4 and, over time, improve muscle strength.

The goals of this clinical trial are to study the safety and efficacy of bidridistrogene xeboparvovec.

The assessment of the potential risks for human health and the environment linked to the deliberate release

- The vector that is intended to deliver the corrected gene to cells is a type of virus, but it is different from a normal virus. Normal viruses (such as the flu) get into the body, attach to cells, and make copies of themselves, which leads to an infection. Scientists altered this virus so that it is not expected to make copies of itself and cause an infection once it is inside the body. The only function of a virus that is retained is its ability to seek out and attach to cells in the body. That is why scientists call this virus a vehicle, or a viral vector. It is intended to carry the corrected gene to the cells that need it.
- The viral vector in bidridistrogene xeboparvovec was made from a type of virus called an **adeno-associated virus (AAV)**. These viruses are found in nature. They can infect humans, but don't typically cause sickness or disease. On its own, the bidridistrogene xeboparvovec viral vector is not expected to reproduce itself. The only way this might happen is if there were certain other viruses present in the body, including another AAV. In the unlikely event that this happened, there is no evidence to suggest this would pose a threat to human health.
- Bidridistrogene xeboparvovec uses a viral vector to add the beta-SG gene to the body. Some vectors can be passed through bodily fluids (whole blood, serum, urine, saliva) for several weeks after an infusion. This process, called vector shedding, is why participants should follow special guidelines for at least 4 weeks after their infusion. The risk of transmission by viral shedding is expected to be minimal because the viral vector is unlikely to reproduce and because it is not expected to survive outside the treated participant. However, as part of this clinical trial (and any future trials with bidridistrogene xeboparvovec), trial doctors and researchers will keep track of potential effects of viral shedding.
- One of the potential concerns about gene therapy in general is whether there is potential to cause unwanted genetic mutations, including mutations that might lead to the development of cancer cells. The research done to date (in rats, dogs, monkeys, and humans) suggests this is a rare occurrence with viral vectors. In addition, research done to date with bidridistrogene xeboparvovec, both in the lab and in clinical trials, show no evidence of tumor development after treatment, even after long-term follow-up. The effects of bidridistrogene xeboparvovec are expected to be limited to the treated individuals. There is no known risk of passing on any genetic mutations to future generations.
- The bidridistrogene xeboparvovec viral vector was not designed to contain any parts of a virus that would allow it to reproduce itself. It also was designed not to contain any potentially harmful genes. Bidridistrogene xeboparvovec was designed to deliver a gene that will help only to make a protein already present in a healthy human body, so the treatment is not expected to be toxic to people. Research done to date shows no evidence of toxic effects when bidridistrogene xeboparvovec is given at the dose that will be used in this trial.

- In clinical trials studying bidridistrogene xeboparvovec to date, there have been no concerning immune responses to treatment. Immune responses have been monitored, managed, and reversible. Participants will receive a type of medication called a steroid to minimize the immune response to AAV therapy. Participants will also be monitored closely, particularly in the first few weeks after treatment, when the risk of an immune response is greatest.

The proposed measures to limit the potential risks, to control and to ensure follow-up of the deliberate release

Healthcare providers and onsite personnel will be trained in best safety practices to be applied during preparation of bidridistrogene xeboparvovec in the pharmacy, transport to the treatment room, precautions during infusion, and disposal of the product.

The training also involves teaching healthcare professionals to wear protective clothing when administering treatment, having equipment available to clean up any spills safely, and properly disposing of medical waste.

Bidridistrogene xeboparvovec will be shipped to trial sites in line with standard recommendations for the safe transport of experimental gene therapies.

Only participants enrolled in the clinical trial may receive bidridistrogene xeboparvovec, and only authorized personnel may supply or infuse bidridistrogene xeboparvovec. All trial drugs must be stored in a secure, environmentally controlled, and monitored area in accordance with the labelled storage conditions, with access limited to authorized site staff.

The trial physician is responsible for trial drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). It is not expected that bidridistrogene xeboparvovec will be deliberately released into the environment outside the administration site. The risks related to the release into the environment (for example, if is a breach with the packaging and/or storage or accidental spillage at the site or during shipping/storage) are expected to be negligible.

Instructions will be provided to participants' families and caregivers regarding use of protective gloves if/when coming into direct contact with participant's bodily fluids and/or waste, as well as using good hand hygiene for a minimum of 4 weeks after the infusion of bidridistrogene xeboparvovec.

Additionally, participants are prohibited from donating blood for 2 years after receiving bidridistrogene xeboparvovec.

Confidentiality of participant information

Information learned about participants during this clinical trial will be maintained confidentially by the trial staff. Any information that is collected or reported will use a participant number identifier instead of the participant's name. Only the trial doctor and the trial staff are able to match the number with the participant's name. To participate in this trial, participants must allow the trial team to use their health information, including information obtained directly from the participant or gathered from their existing medical records. If a person does not want the trial doctor to use their health information, that person may not participate in this trial.