Information for the public

Short trial title: GenePHIT: A study to learn more about how well a new gene therapy (AB-1002) works and its safety in participants with congestive heart failure

Full trial title: A Phase 2, adaptive, double-blinded, placebo-controlled, randomized, multi-center trial to evaluate the efficacy, safety and tolerability of intracoronary infusion of AB-1002 in adult subjects with New York Heart Association (NYHA) Class III heart failure and non-ischemic cardiomyopathy

EU clinical trial number: 2024-510581-17-00

Brief description of the project

Congestive heart failure (CHF) is a condition where the heart is unable to pump blood as effectively as it should. This leads to a buildup of fluid in body tissues causing shortness of breath, tiredness, and swelling in the abdomen and legs. For people with severe heart failure, there are limited treatment options, and sometimes advanced treatments such as heart transplants or other surgical procedures may be required. Thus, there is a need for new treatment options for people with CHF.

AB-1002 is a gene therapy currently being studied in people with CHF. Gene therapy introduces a functioning gene into a person's cells to treat their disease. AB-1002 improves the levels of calcium in the cells of the heart, preventing further changes in the structure and function of the heart, and increasing the ability of the heart to pump blood effectively.

These effects may help to improve the function of the heart and the overall well-being in people with CHF.

Description of the genetically modified organism (GMO)

AB-1002 is an experimental gene therapy currently being studied in people with congestive heart failure. Gene therapy introduces a functional gene into a person's cells to treat their disease. It also includes a transport vehicle (also called a vector) that is intended to protect the gene and deliver it to the cells.

AB-1002 uses a recombinant (made in a laboratory) virus called adeno-associated virus or AAV. AAV is not associated with any known diseases in humans and is not able to replicate. AAV is used as a vehicle to deliver a gene coding for the constitutively active form of the protein phosphatase 1 Inhibitor 1 (I-1c) which helps improve the way calcium is used within the heart muscle cells so that the heart can pump blood more effectively and supply enough blood to all the organs of the body. Approximately 90 to 150 participants are planned to be treated in this study at several different locations in Europe, United Kingdom, Canada and the United States, including approximately 5 participants in Belgium.

What treatments will the participants get?

- **AB-1002 (the study drug)**: Participants will receive AB-1002 at 2 different dose levels (low dose or high dose) as a single infusion directly into the main arteries supplying blood to the heart.
- **Placebo**: This looks similar to the study drug AB-1002 but does not have any medicine in it. Participants will receive it in the same way as the study drug.

The participants will also receive their regular heart medications and drugs to improve the radiology assessments.

In order to administer the treatment a narrow tube called a catheter is inserted into the blood vessels of the groin or wrist and directed towards the heart. This procedure is usually done under local anesthetic. The doctor administering the drug will use x-rays to help them guide the tube to the correct position in the blood vessels of the heart. Before administering AB-1002 or placebo, the doctor will administer a special dye (called contrast) to see the blood vessels of the heart clearly in the x-ray images. This part of the procedure is called an angiogram. The doctor performing the procedure will also administer another medicine (nitroglycerin) during the procedure to increase the blood flow through the blood vessels of the heart.

How long will participants be in the trial?

Participants will be in the trial for up to 61 months (about 5 years). This includes 1 month before treatment and 5 years after treatment. In Belgium, the trial will start approximately in August 2025 and end approximately in December 2030.

Where will this trial take place?

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

Organisation Name:	*AZORG*
Address Details:	Moorselbaan 164 9300 Aalst Belgium

Organisation Name:	*Universitair Ziekenhuis Antwerpen*
Address Details:	Drie Eikenstraat 655 2650 Edegem

Organisation Name:	Universitair Ziekenhuis Gent
Address Details:	Corneel Heymanslaan 10 9000 Gent

Organisation Name:	*Algemeen ziekenhuis Delta*
Address Details:	Deltalaan 1 8800 Roeselare

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

AB-1002 is intended to increase expression of I-1c in patients with congestive heart failure (CHF). These effects may help to improve the function of the heart and the overall well-being in people with CHF. The goals of this clinical trial are to study the safety and efficacy of AB-1002.

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 AB-1002 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, AB-1002 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.
- AB-1002 uses a viral vector to add the I-1c 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 is called vector shedding. 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, 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 AB-1002, both in the research laboratory and in clinical trials, show no evidence of tumor development after treatment. The effects of AB-1002 are expected to be limited to the treated individuals. There is no known risk of passing on any genetic mutations to future generations.
- AB-1002 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. AB-1002 was designed to deliver a gene that will help only to make a constitutively active form of a protein already present in a healthy human body, so the treatment is not expected to be toxic to people.

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 AB-1002 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.
- AB-1002 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 AB-1002, and only authorized personnel may supply or infuse AB-1002. 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 pharmacist is responsible for trial drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). It is not expected that AB-1002 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.
- Recommendations will be provided to participants' families and caregivers after the administration of AB-1002 regarding reminder on good hand hygiene practice e.g hand washing after going to the bathroom and before eating and barrier methods of contraception for a minimum of 6 months after receiving the experimental gene therapy.
- Additionally, participants are advised to refrain from donating blood, sperm, cells and tissues after the administration of AB-1002.