Framework of research and development for a proposed Deliberate Release of a Genetically Modified Organism

GNT-016-MDYF

Microdystrophin (GNT0004) Gene Therapy Clinical Trial in Duchenne Muscular Dystrophy: A phase I/II/III study with a dose determination part followed by an efficacy and safety evaluation, quadruple blind placebo-controlled part and then by a long-term safety follow up part, in ambulant boys.

1. **Description of the genetically modified organism**

GNT0004 is a recombinant adeno-associated parvovirus (AAV) vector in which the wild-type AAV replication and capsid (protective shell of a virus) genes have been removed and replaced with the hMD1 expression cassette. The intended outcome of the genetic modifications in GNT0004 was to generate a vector which would be replication- incompetent and serve only to introduce functional transgene encoding the hMD1 gene to patients with Duchenne Muscular Dystrophy (DMD) who have dystrophin gene mutation.

This gene therapy is intended to provide DMD patient, whatever their genetic defect, an optimized microdystrophin protein. Although shorter than the full length dystrophin, this microdystrophin has been engineered to retain key functional domains and has demonstrated the ability to significantly delay or markedly slow down the disease progression in rodent and canine DMD models. Thus, as GNT0004 lacks the capsid and replication genes required for viral replication and particle formation, it is unable to produce itself. Its function will deliver an optimized microdystrophin protein to DMD patients.

2. **The nature and goal of the foreseen deliberate release**

GNT0004 is to be released for the purpose of a clinical trial (protocol GNT-016-MDYF) to determine the efficacy and safety, of a single peripheral intravenous (IV) infusion of GNT0004 to patients with Duchenne Muscular Dystrophy.

3. **Assessment of the potential risk for human health and the environment linked to the deliberate release**

GNT0004 is infused directly to the subject in the hospital. It is only expected to be shed in a participant his bodily fluids to a limited extent. In addition, as GNT0004 vector is non-replicative, shed viral particles transmission and gene transfer to organisms other than the study subjects is considered unlikely. Therefore, due to the incapacity of replication, the non-infectious nature of the shed DNA and the negligible amounts shed, the risk to the environment can be considered negligible.

4. **Proposed measures to limit the potential risk, to control and ensure follow-up of the deliberate release**

GNT0004 is an investigational drug shipped to sites in 4 mL type I glass vials (primary container) containing 2.5 mL of product stored in frozen form at a -80°C ± 10°C. Each IMP vial is packaged in an individual sealed box (secondary packaging). The required number of GNT0004 vials are shipped by

a specialized courier from the manufacturing site to the unblinded Pharmacist or designee at clinical trial site in line with standard recommendations for the transport of biohazardous materials.

Since GNT0004 is considered Biosafety Level 1 (BSL-1) and is used in a clinical trial, it's usage will be restricted to hospital facilities which will have been audited for dealing with biologic hazardous and infectious material, including storage and waste management. All involved personnel at the site will be trained in best biosafety practices to be applied during thawing, transport to the administration room, precautions during administration and disposal of any biological waste.

The Sponsor will also provide the site with a pharmacy Manual that includes directions for documenting the control of the IMP from the time of receipt at the trial site until final accountability and destruction. In addition, it describes the required processes for managing and documenting any issues. The risks related to the release into the environment of the GMO or risks to personnel in the event there is a breach in container integrity and/or storage or accidental spillage at the site or during shipping/storage, is considered to be negligible.

GNT0004 will only be handled by trained personnel and in the event that a spillage and/or accidental exposure did occur, the product is non-pathogenic and non-replicative, limiting spread and risks to the environment or personnel.

Personnel handling GNT0004 will wear personal protective equipment (PPE) (laboratory coats, gowns, gloves and safety glasses) in line with standard local procedures for BSL-1 products. An appropriate spill kit will be available in the areas where GNT0004 is prepared and administered in line with standard local procedures for BSL-1 products.

Established standard local procedures for handling potential biohazardous materials such as patient samples/fluids and medical waste (autoclaves, sharps bins, incinerators, disinfectants, and appropriate cleanable surfaces) will be followed.

As GNT0004 is non-replicative, shed viral particles are unable to multiply and thus, the spread of the GMO is inherently limited.

5. **Date and location of release**

Start & end date of the study in Belgium: April 2026 – November 2031

Estimated number of patients in Belgium: 10

Locations of release:

Universitair Ziekenhuis Leuven
Herestraat 49
3000 Leuven

Brussels University Hospital - Queen Fabiola Children's University Hospital
Avenue Jean Joseph Crocq 15
1020 Brussels