Framework of research and development

Title of the study:

A Phase 1/2 Ascending Dose Study to Evaluate the Safety and Effects on Progranulin (PRGN) Levels of PR006A in Patients with Fronto-Temporal Dementia with Progranulin Mutations (FTD-GRN)

Brief description of the project:

The Genetically Modified Organism (GMO) will be investigated in a Phase 1/2 study to evaluate the safety and effects of a single intracisternal magna (ICM) injection of PR006A in adult participants with Fronto-Temporal Dementia with Progranulin Mutations (FTD-GRN) for the study duration of ~5 years. Three escalating dose cohorts are planned with a maximum of 1.4×10^{14} vg of PR006A. Approximately 15 participants will be dosed with PR006A worldwide.

Primary objective is to evaluate the safety, tolerability and immunogenicity of 3 dose levels of PR006A administered via suboccipital injection into the cisterna magna and to quantify progranulin (PGRN) levels in blood and cerebrospinal fluid (CSF).

Preclinical studies:

Nonclinical pharmacology was evaluated in human cell culture test systems, in an established genetic mouse model, and Cynomolgus monkeys.

Intracerebroventricular (ICV) injection of PR006A effectively transduced the genetic mouse model, resulting in robust, dose-dependent expression of the transgene, as evidenced by production of progranulin messenger ribonucleic acid (mRNA) and protein in the central nervous system (CNS). This reduced many of the phenotypes that occur in the brain of this FTD-GRN mouse model.

PR006A was evaluated *in vivo* in Cynomolgus monkeys. Progranulin was expressed in the monkeys and the results of the Non-Human Primate (NHP) studies indicate no safety or toxicity concerns. All animals survived until their scheduled necropsy date, and postmortem pathology analysis indicated no adverse toxicity concerns.

Description of the GMO

PR006A is a non-replicating recombinant vector derived from adeno-associated virus containing a codon-optimised version of the human gene coding for progranulin, that may be effective for the treatment of patients with FTD-GRN.

It is expected that administration of PR006A will result in sustained production of progranulin to slow or halt the progression of disease.

The nature and goal of the foreseen deliberate release

The deliberate release of PR006A is associated with vector shedding from patients who were administered with it.

Recombinant adeno-associated virus (AAV) vector shedding is commonly observed in studies involving AAV based vectors. Shedding occurs at very low levels and, taking into consideration that PR006A is unable to replicate, is not considered as posing a risk to people and the environment. Shedding of PR006A will be carefully assessed during the Phase 1/2 clinical study.

PR006A is being tested as a potential gene therapy for Fronto-Temporal Dementia with Progranulin Mutations. It is hypothesized that the administration of PR006A to patients with FTD-GRN will result in slowing or halting of the patients' disease progression.

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

The release of PR006A as described in this application is not expected to result in adverse environmental impact, including the human patient population, for the following reasons:

1. Lack of pathogenicity of the parental virus and the GMO: Despite an estimated seroprevalence of ~80% for some common human serotypes, no pathogenic effects of AAV have been identified. The modifications which have led to the generation of the GMO have not raised the pathogenicity (see point 6. below).
2. Replication-incompetent GMO: PR006A is a non-pathogenic recombinant AAV vector that lacks all AAV viral genes and cannot replicate without AAV-specific helper functions and helper virus activities. PR006A replication could only occur in the extremely unlikely event of a host cell being infected by wild-type AAV and a helper virus such as human adenovirus or herpes simplex virus. If replication occurred, the only expected products would be PR006A and wild-type (WT) AAV, both intrinsically non-pathogenic viruses.
3. Risk of transmission by viral shedding: PR006A is replication-incompetent and is not expected to survive, multiply or disperse if it were to be eliminated intact from the treated patient. AAV-based gene therapies are known to shed via bodily fluids. It has been shown consistently that vectors are shed for a short period of time following administration, but then become undetectable in bodily fluids. The viral load shed in bodily fluids is expected to be low, compared to the necessary dose required to achieve detectable gene expression in humans. Viral shedding, i.e., excretion/secretion of viral particles that could be transmitted to other individuals, will be assessed in saliva, urine, and stool samples. Analysis of samples will continue until 3 consecutive data points are obtained at or below the limit of detection of the shedding assay. If the level of shedding does not reach the limit of detection of the assay but there is a continual decreasing trend, collection should continue until the results demonstrate that a plateau has been reached in at least 3 consecutive data points.

   Minimal exposure to PR006A, such as environmental exposure, of persons other than study participants would not be of sufficient dose to result in significant gene expression in humans. Other than potential human hosts, exposure to PR006A is not expected to affect any non-target organisms, either directly or indirectly.

4. Minimal risk of insertional mutagenesis: Data from various model organisms and humans indicate that the integration of AAV vectors into the genome is a rare event, where the bulk of the vector is assimilating into concatemeric episomes. Unlike retroviral vectors, which encode viral proteins to create double-stranded breaks, when AAV integration does occur, it does so at pre-existing chromosomal breaks. The results of integration are deletions in the AAV inverted terminal repeats (ITRs) and duplications of host sequences. No clinical trials to date with AAV have reported incidences of insertional mutagenesis.
5. Tissue-specific transgene expression: PR006A is injected via suboccipital injection into the cisterna magna in a single administration and shows a strong tropism for the CNS. Transduction of non-target cells is possible, but will not pose a safety risk.
6. Minimal risk associated with the transgene: The viral vector does not contain any viral sequences, except ITRs which facilitate transgene expression, and does not lead to production of viral proteins, particles or deoxyribonucleic acid (DNA) replication. Comprehensive toxicity studies did not demonstrate a toxic effect of PR006A. The protein encoded by the transgene is a naturally occurring protein and is therefore unlikely to be toxic to humans or other organisms. No genes for toxins, potential oncogenes, growth factors or other genes that could be potentially harmful have been inserted into the GMO. With administration of PR006A to humans, the only foreign proteins that the immune system will be exposed to are the viral capsid proteins.

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

PR006A will be shipped to study sites in line with standard recommendations for the transport of biohazardous materials. PR006A will be stored, prepared and administered by trained medical professionals, in a hospital setting only, to patients that meet criteria for inclusion into the clinical study. Staff will follow the waste and disposal policies as per national and local site requirements to dispose of consumables used in the preparation and administration of the GMO. The use of needles will be kept to a minimum.

A Pharmacy Manual and training material located at sites provides pharmacy personnel and clinical medical staff directions on use, storage and destruction of the investigational medicinal product (IMP). It also 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, such as shipment or storage, temperature excursions and reporting of technical product complaints. 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. The GMO will only be handled by delegated, trained personnel and in the event that a spillage did occur, the product is non-pathogenic and non-replicative, limiting spread and risks to the environment or personnel.

Patients will receive PR006A by a one-time injection in a clinical setting. Viral vector shedding will be assessed in this study, as described above. As PR006A is non-replicative, shed viral particles are unable to multiply and thus, the spread of the GMO is inherently limited.

Local procedures and guidelines for the management and disposal of a Risk Group 1 product should be followed by all personnel responsible for transporting, preparing, administering, disposing of PR006A IMP or equipment/consumables that have come into contact with the product designated for use in clinical study. **Table 1** summarizes the procedures that will be used by staff to manage incidents related to PR006A.

Site name and location in Belgium*:* UZ Leuven; Herestraat 49, 3000 Leuven, Belgium

Estimated number of patients in Belgium: 2

Start and End date of the study in Belgium: October 2021 until January 2028

Table 1: Management of incidents related to PR006A product

Incident	Procedure
Accidental spillage	Any surfaces contaminated with PR006A will be decontaminated using an appropriate viricidal agent, such as a 1:10 dilution of bleach, for 10 minutes. Upon completion of this contact time, the area may be cleaned according to standard local procedures. Follow decontamination with a 1:1 cycle of sterile water and 70% isopropyl alcohol (IPA). This process should be discussed with the local environmental health and safety officer and/or biosafety committee before receipt of any PR006A product on site so that an appropriate plan and supplies are in place.
Sharps injury	The use of needles is to be kept to a minimum. In the event of injury, follow local institutional procedures and report to Principal Investigator (PI). PI to notify Clinical Research Associate (CRA).
Contact with skin and clothing	Remove contaminated clothing. Flush area with large amounts of water. Use soap. Seek medical attention,
Contact with eyes.	Flush with water while holding eyelids open for at least 15 minutes. Seek medical attention immediately.

PR006A is stored in single use 2 mL closed vials, each containing 1 mL extractable volume. Staff will be advised that care must be taken when manipulating vials and that the use of needles should be kept to a minimum. In the event of injury, staff will follow local institutional procedures.