Framework of Research and Development

Title of the study:

A Phase 1/2 Investigation of Novel Experimental Regimen in Amyotrophic Lateral Sclerosis (PIONEER-ALS): An Open-Label, Uncontrolled, Multicenter Study to Assess the Safety and Tolerability of Two Doses of VTx-002.

Brief description of the project & Framework of Research/Development:

The Genetically Modified Organism (GMO) will be investigated in a Phase 1/2, to evaluate the safety, tolerability and effects on clinical and biomarker endpoints of intracisternal administration of VTx-002 in participants with Amyotrophic Lateral Sclerosis (ALS). Two escalating dose (low dose and high dose) cohorts are planned. The duration of the study will be a maximum of 5 years and 5 weeks (265 weeks) for each participant. Approximately 12 participants will be dosed with VTx-002 worldwide.

The primary objective of this Phase 1/2 clinical study is to assess the safety and tolerability of two doses of VTx-002 administered via intracisterna magna injection in adult participants with amyotrophic lateral sclerosis (ALS). Secondary and exploratory objectives include evaluating the effects of VTx-002 on clinical and biomarker endpoints, viral shedding, and additional analyses of pharmacodynamic and preliminary efficacy measures.

Study results are expected to inform further research and development of VTx-002 and ALS.

Description of the GMO:

VTx-002 is a non-replicating recombinant vector derived from adeno-associated virus (AAV), containing a humanized anti-TDP-43 single chain variable fragment (scFv) transgene expression cassette. This transgene is designed to bind pathological forms of TDP-43, a nuclear transcriptional repressor whose dysregulation is a hallmark of ALS pathology.

Nature and goal of the foreseen deliberate release:

The deliberate release of VTx-002 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 VTx-002 is unable to replicate, is not considered to pose a risk to people and the environment. Shedding of VTx-002 will be carefully assessed during the Phase 1/2 clinical study.

VTx-002 is being tested as a potential therapy for treatment of ALS. It is hypothesized that administration of VTx-002 will result in sustained intracellular production of the anti-TDP-43 scFv, aiming to slow or halt the progression of ALS by targeting the underlying pathology.

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

The release of VTx-002 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: VTx-002 is derived from Adeno-Associated Virus (AAV) serotype 5, which belongs to the Dependovirus genus. AAVs are non-pathogenic and are not associated with any disease in humans. The parental virus and the genetically modified organism (GMO) used in VTx-002 do not cause illness and are considered safe for clinical use.
2. Replication-incompetent GMO: VTx-002 is an AAV-based vector that is replication-incompetent. It cannot replicate in the absence of a helper virus and is engineered to prevent replication entirely. This means that after administration, the vector cannot multiply or spread beyond the intended target cells.
3. Low risk of transmission by viral shedding: VTx-002 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. Viral shedding, i.e., excretion/secretion of viral particles that could theoretically be transmitted to other individuals, will be assessed as part of the clinical study, though, minimal exposure to VTx-002, 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 VTx-002 is not expected to affect any non-target organisms, either directly or indirectly.
4. Tissue-specific transgene expression: VTx-002 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 is not anticipated to pose a safety risk.
5. Minimal risk associated with the design of VTx-002: None of the incorporated elements are considered toxic or harmful to humans or other hosts, and the expression cassette does not confer traits to the vector that enhance survival, persistence, or invasiveness in the environmental ecosystem. Further, comprehensive toxicology studies did not demonstrate a toxic effect of VTx-002 at doses similar to and above the planned clinical doses.

Potential advantages of the deliberate release:

Potential advantages of the deliberate release of VTx-002 include:

1. Therapeutic benefit for ALS patients: VTx-002 is designed as a first-in-class, disease-modifying gene therapy for ALS. Its deliberate release enables clinical evaluation of a

novel approach targeting TDP-43 pathology, which is implicated in the majority of ALS cases. The therapy aims to provide sustained intracellular production of an anti-TDP-43 antibody fragment, potentially slowing or halting disease progression. There currently is a large unmet need for a therapy that slows or halts ALS disease progression.

2. Advancement of scientific knowledge: The deliberate release allows for the collection of critical safety, tolerability, pharmacodynamic, and preliminary efficacy data in humans. This supports the development of new gene therapies and advances understanding of ALS biology and vectorized antibody approaches.

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

VTx-002 will be shipped to study sites in accordance with standard recommendations for the transport of biohazardous materials. At the clinical site, VTx-002 is stored at ≤ -65°C in a dedicated, secured freezer with restricted access and continuous temperature monitoring. The investigational product is handled exclusively by trained pharmacy and clinical staff, following Biosafety Level 1 measures and national legislation. Every transport step—from pharmacy to dose preparation and administration—is documented in a chain of custody log, and all containers are disinfected and clearly labelled to ensure traceability and biosafety compliance. Preparation of the dose (thawing, dilution, mixing, filtering) is performed under a biosafety cabinet in a cleanroom, and administration is by a one-time intracisternal magna injection in a hospital setting.

All involved personnel are trained in biosafety practices, including the use of personal protective equipment, spill kits, and validated decontamination procedures. Waste and unused investigational product are disposed of as clinical waste or incinerated according to local policy and biosafety requirements. Non-disposable materials and surfaces are disinfected with agents proven effective against AAV.

Standard hospital hygienic measures are applied during sampling, handling, and storage of patient samples, which are kept in closed containers with restricted access and monitored storage conditions.

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

Estimated number of patients in Belgium: Up to 3 patients

Start and end date of the study in Belgium: May 2026 until ~December 2031