Framework of research and development for a proposed

Deliberate Release of a Genetically Modified Organism

Clinical trial SPVN20-CLIN-01: An Open-Label Dose-Escalation Study to Assess the Safety and Tolerability of a Single Intravitreal Injection of SPVN20 Gene Therapy in Subjects with No Light Perception Due to End-Stage Rod-Cone Dystrophy, and Who Retain Dormant Foveal Cone Photoreceptors

1. Description of the genetically modified organism

SPVN20 or AAVi-GIRK1(F137S) is a nonpathogenic recombinant adeno-associated virus (vector) containing an optimized version of the human gene of G protein-gated inwardly rectifying potassium (GIRK) channel 1. The vector has been engineered to target cone photoreceptors following an intravitreal injection.

2. Purpose of the proposed deliberate release

The purpose of clinical trial SPVN20-CLIN-01 is to study SPVN20 (or AAVi-GIRK1(F137S)) for the treatment of patients with no light perception (NLP) due to end-stage rod-cone dystrophy (RCD), and who retain dormant foveal cone photoreceptors (i.e., cells that have lost their ability for phototransduction). A target of nine (9) subjects will be enrolled in this study, with four (4) subjects expected to be enrolled in Belgium. SPVN20 will be administered to patients in the eye via the intravitreal route. In the SPVN20 treatment approach, GIRK1(F137S) transgene is expressed in dormant foveal cone photoreceptors, to restore their ability for phototransduction. Following SPVN20 administration to patients with NLP due to end-stage RCD, GIRK1(F137S) expression in dormant cones could provide an alternative hyperpolarization mechanism in response to light stimulus, in the form of an alternative phototransduction cascade, allowing cone reactivation.

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

Administration of SPVN20 will occur only within contained clinical sites by trained medical professionals. The clinical vector SPVN20 is replication incompetent by design and will not contain any replication-competent (helper) virus sequences. Viral shedding in the body fluids (whole blood, urine, tears) from patients who receive SPVN20 as part of the clinical trial will be closely monitored. Even if release would occur, the GMO will not be able to spread in the environment. In the case of accidental exposure and transfer of vector to an unintended human or non-human recipient, the risks are considered negligible since the vector is not able to replicate, is not known to be pathogenic, and the amount of particles is unlikely to cause significant infections in the exposed individual. Therefore, environmental impact of SPVN20 is considered to be negligible.

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

SPVN20 will be shipped to study sites in line with standard recommendations for the transport of biohazardous materials. SPVN20 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 of accidental exposure, such as breach in container integrity and/or storage or accidental spillage at the site or during shipping/storage, are 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 by design, limiting spread and risks to the environment or personnel. Appropriate decontamination should be performed, as per local site requirements, in case of spillage. The risks related to release into the environment of the GMO due to shedding is also considered to be negligible. Patients will receive SPVN20 by a one-time injection in a clinical setting. Viral vector shedding has been assessed as part of nonclinical studies conducted in animals, and will be assessed in humans in this study, as described above. Shedding is anticipated to be minimal and transient. As SPVN20 is non-replicative by design, potential shed viral particles will be 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 SPVN20 IMP or equipment/consumables that have come into contact with the product designated for use in clinical study.

5. Date and location of release

Site name and location in Belgium: Department of Ophthalmology at the Ghent University & Ghent University Hospital, located C. Heymanslaan 10, 9000 Gent, Belgium

Estimated number of patients in Belgium: 4

Start and End date of the study in Belgium: July 2025 to July 2031 (includes a five-year follow-up period)