Common application form for investigational medicinal products for human use that contain or consist of AAV vectors[1]

Note 1: This application form can be used for submissions in the following jurisdictions: Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Portugal, Romania, Slovenia and Spain.

Note 2: The application form must be accompanied by the SNIF (summary notification information format for notifications concerning the deliberate release into the environment of genetically modified organisms for purposes other than for placing on the market)[2] in the case of submissions that are made under Directive 2001/18/EC.

Document history	Publication date	Description of main changes
Version 1	October 2019	
Version 2	December 2020	Endorsement by additional Member States (LT, SI)
Version 3	January 2022	Endorsement by an additional Member State (EE) and NO

[1] This document has not been adopted by the European Commission and, therefore, it does not contain the official position of the European Commission.

[2] Council Decision 2002/813/EC establishing, pursuant to Directive 2001/18/EC of the European Parliament and of the Council, the summary notification information format for notifications concerning the deliberate release into the environment of genetically modified organisms for purposes other than for placing on the market (OJ L 280,18.10.2002, p.62).

1. Introduction

Clinical trials conducted in the EU with investigational medicinal products that contain or consist of genetically modified organisms ("GMOs"[3]) must comply with the legislation governing the authorization of clinical trials.[4]

Clinical trials with medicinal products that contain or consist of GMOs must also comply with applicable requirements under Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms[5] ("deliberate release framework") and/or under Directive 2009/41/EC on the contained use of genetically modified micro-organisms ("contained use framework").[6]

This application form implements the requirements of the Directive 2009/41/EC and of the Directive 2001/18/EC, as adapted to the specific characteristics of adeno-associated viral vectors ("AAVs") contained in investigational medicinal products for human use.

This is an application form for investigational medicinal products for human use that contain or consist of AAVs (hereafter referred to as "clinical vectors"). However, if the application concerns an investigational medicinal product that contains or consist of AAVs that has already been granted a marketing authorisation, the *submission form for use in case of clinical trials with authorised medicinal products* should be used (provided that the submission form has been endorsed by the competent authorities in the relevant jurisdiction).

The application form has been endorsed by Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Portugal, Romania, Slovenia and Spain.

2. Explanatory notes

The common application form is without prejudice to consultation requirements that exist under Directive 2001/18/EC.

In addition, certain national requirements may need to be considered by developers of medicinal products before they submit the application form to the relevant competent authorities:

Austria:

Applicants should send separate submissions in case there are multiple sites concerned in Austria (including clinical premises, laboratories in which activities with GMOs are carried out, locations of storage of the

[3] Throughout this document, the term "GMO" should be understood as covering both genetically modified organisms as defined under Article 2(2) of Directive 2001/18/EC, and genetically modified micro-organisms within the meaning of Article 2(b) of Directive 2009/41/EC.

[4] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC, (OJ L158, 27.5.2014, p.1). Until the Regulation applies, Directive 2001/20/EC is applicable (Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L121,1.5.2001, p.34).

[5] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (OJ L 106, 17.4.2001, p. 1).

[6] Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (OJ L 125, 21.5.2009, p. 75).

investigational medicinal product and location of storage of samples from clinical trial subjects that contain GMOs).

Further information is available at:
https://www.sozialministerium.at/site/Gesundheit/Gentechnik/Rechtsvorschriften_in_Oesterreich/

Belgium:

The common application form should be part of a biosafety dossier submitted by each of the clinical sites where the investigational medicinal product will be administered. However, one person (*e.g.* the sponsor) can be empowered by the concerned sites to submit all the necessary notifications, provided that the person responsible for the activity is clearly indicated in the form.

More information on procedural requirements and forms for the three regions is available at:
https://www.biosafety.be/content/contained-use-gmos-andor-pathogenic-organisms-notification-procedures.

Czech Republic:

Each clinical site as well as other institutions where the activities with GMOs will take place (*e.g.* laboratories that are not premises of one of the clinical sites) should submit a separate notification for deliberate release or for contained use, as appropriate. However, one person (*e.g.* the sponsor) can be empowered by the concerned sites/institutions to submit all the necessary notifications.

France:

For investigational medicinal products that are assessed under the contained use framework, applicants should send separate submissions in case there are multiple sites concerned in France.

Italy:

For investigational medicinal products that are assessed under the contained use framework, each clinical site (including clinical premises, laboratories in which activities with GMOs are carried out, locations of storage of the investigational medicinal product and location of storage of samples from clinical trial subjects that contain GMOs) should submit a separate notification. However, one person (*e.g.* the sponsor) can be empowered by the concerned sites/institutions to submit all the necessary notifications.

It is stressed that, in case the submission is made by a third party on behalf of the site, the responsibilities of the site holders and users concerned (as set out under Legislative Decree n. 206/2001) remain unchanged.

The Netherlands:

More information on national procedural requirements and forms is available at: https://www.loketgentherapie.nl/en/aav

COMMON APPLICATION FORM FOR INVESTIGATIONAL MEDICINAL PRODUCTS FOR HUMAN USE THAT CONTAIN OR CONSIST OF AAV VECTORs

SECTION 1 – ADMINISTRATIVE INFORMATION

1.1. Identification of the applicant.

Organisation Name:	SparingVision
Address Details:	5-7 avenue Percier 75008 Paris
Contact person:	Sophie Skorupka Associate Director, Regulatory Affairs
Telephone No:	+33 (0)1 43 46 20 60
Email Address:	sophie.skorupka@sparingvision.com

1.2. Identification of the sponsor (to the extent that is different from the applicant).

Organisation Name:	Please refer to applicant information.
Address Details:	
Contact person:	
Telephone No:	
Email Address:	

1.3 Identification of the manufacturer of the clinical vector.

Organisation Name:	MassBiologics (MBL) Service provided: SPVN20 DS Manufacture
Manufacturing location:	1240 Innovation Way, Fall River, MA, 02720, USA

Organisation Name:	Thermo Fisher Scientific Viral Vector Services (VVS) Service provided: SPVN20 Drug Product Manufacture
Manufacturing location:	5 Commerce Boulevard, Plainville, MA 02762, USA

Organisation Name:	Clinigen Clinical Supplies Management s.a. Service provided: Secondary packaging, labelling, distribution

Manufacturing location:	Watson and Crick Hill, Rue Granbonpre 11, Mont-Saint-Guibert, 1435, Belgium

Organisation Name:	Clinigen Clinical Supplies Management GmbH Service provided: IMP qualified person (QP) certification
Manufacturing location:	Am Kronberger Hang 3, Schwalbach Am Taunus, 65824, Germany

SECTION 2 –INFORMATION RELATING TO THE INVESTIGATIONAL MEDICINAL PRODUCT

2.1. Description of the production system.

Clear maps of the vectors used for recAAV production (e.g. plasmids, baculoviruses) showing all the constituent parts of the AAV clinical vector should be provided (i.e. in addition to the "transgene vector", all other vectors such as helper, packaging and pseudotyping vectors should be described).

The characteristics of all cell lines used and eventual modifications of the cell genome should be explained. Describe the cell type(s) concerned as well as their origin (e.g. human kidney, epithelial cells, insect cells).

The possibility of the genetic material in the cells/cell lines causing a certain interaction with the clinical vector, such as by complementation or recombination should be discussed. In particular, the tests applied to identify possible contamination of the cell line by wild-type AAV viruses and/or any virus identified as helper virus for AAV should be explained.

The active substance of SPVN20 (AAVi-GIRK1(F137S)) consists of an adeno-associated virus (AAV) engineered vector capsid, encapsidating a transgene that encodes for a mutated form of the human GIRK1 (GIRK1(F137S)), a G-protein-gated inward rectifier potassium (K+) channel (GIRK).
The SPVN20 drug substance (DS) is manufactured according to current good manufacturing practice (cGMP) following a standard AAV manufacturing process using transient triple plasmid transfection (transfer, packaging, and helper plasmids) of a human embryonic kidney (HEK293) producer cell line in suspension.

Please refer to the confidential CAF for additional details on cell lines and plasmids.

2.2. Demonstration of absence of formation of replication-competent virus.

The risk of generation of a replication competent AAV through recombination of the constituent parts of the viral vector system should be minimised. Test methods for detection of replication-competent virus should be described including information on the specificity and sensitivity thereof. Data from RCV testing at different manufacturing steps should be provided (e.g. virus seed bank, final product). Release criteria with regard to RCV testing should be specified.

Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.

Wild-type AAV (wtAAV) genome contains two genes for capsid formation (cap gene) and DNA replication and packaging (rep gene). In order to replicate, wtAAV needs a helper virus.
SPVN20 is a recombinant AAV in which wtAAV rep and cap genes are absent. Therefore, even in the presence of a helper virus, SPVN20 would be unable to replicate.

While wtAAV are not associated with any disease in humans, the formation of replication-competent AAV (rcAAV) particles in SPVN20 batches is minimized during SPVN20 manufacturing process:

- The manufacturing process includes transient tri-transfection of HEK293 cells, separating in three different plasmids the AAV Rep/Cap sequences, the adenoviral helper genes required to support AAV replication, and the AAV ITR sequences which constitute the viral origins of replication;
- Plasmids are designed to prevent homologous recombination events.

The presence of rcAAV in SPVN20 batches is controlled at Drug Substance (DS) step by a qualified cell-based assay (using HEK293 cells) and followed by qPCR for the detection of Rep2 DNA. This test is part of the DS lot release specification.

Please refer to the confidential CAF for additional details on acceptance criteria and qualification of the method used.

2.3. Provide a diagram ('map') of the clinical vector.

Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.

The active substance of SPVN20 (AAVi-GIRK1(F137S)) consists of an engineered adeno-associated virus (AAV) vector capsid, encapsidating a transgene that encodes a mutated form of the human GIRK1 (GIRK1(F137S)), a G-protein-gated inward rectifier potassium (K+) channel (GIRK).

Please refer to the confidential CAF for additional details.

2.4. Molecular characterisation of the clinical vector

Provide the annotated sequence of the genome (i.e. indicate the location of the sequences encoding the transgene expression cassette(s) and its regulatory elements).

Describe in what way the clinical vector deviates from the parental virus at the level of molecular characterisation.

Available data supporting genetic stability of the clinical vector should be provided. Deviations should be discussed, in particular the biological significance thereof.

Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.

SPVN20 consists of an engineered AAV vector capsid. Deviations of the clinical vector from the parental virus are described in the confidential CAF. Genetic stability of the clinical vector is monitored and described in the confidential CAF.

2.5. Description of the insert

The expression cassette e.g. transgene, including regulatory and coding sequences, should be described. In particular, it should be explained if the expressed product is toxic or otherwise harmful to humans (other than the clinical trial subject) or other hosts. Additionally, if the applicant considers that the transgene could confer any advantage for replication/survival of the clinical vector (vis-à-vis the parental virus), this should be explained.

Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.

Please refer to the confidential CAF for details on SPVN20 expression cassette.

The transgene protein expressed by SPVN20 (GIRK1(F137S)) is not expected to be toxic or harmful to humans or other hosts, such as primates. Nonclinical toxicology studies have been conducted in healthy non-human primates (NHPs) and no adverse findings were reported.
Furthermore, SPVN20 will be administered intravitreally to eligible patients only, in a hospital setting by trained medical professionals.
The potential for direct exposure will be limited to those medical professionals involved and trained in dose preparation and administration. Procedures are in place to minimise this risk. The likelihood of secondary exposure to close contacts of patients who receive the treatment (including family members, caregivers) is also considered very low, as minimal shedding of the vector was detected in nonclinical biodistribution studies (see section 2.6 for more details).

2.6. Biodistribution and shedding

Detailed data on clinical vector shedding (including information on the administered dose, the route of administration, and –where available- immune status of the treated subjects) from previous clinical trials with the clinical vector should be provided. Where available and if relevant for the environmental risk assessment, biodistribution data should be provided.

If there is no prior clinical experience with the same clinical vector, the potential for shedding should be discussed based on non-clinical data and/or clinical experience from related clinical vectors. If the applicant relies on data from related clinical vectors, the relevance of the data to the product that is the object of this application should be explained considering, in particular, the dose and route of administration.

When shedding occurs, the estimated duration should be specified.

The methods used for detection of viral shedding, including information on the specificity and sensitivity thereof, should be provided.

There is no previous clinical experience with SPVN20.
The SPVN20 shedding profile was assessed as part of the toxicology studies performed in healthy non-human primates (NHPs; African green monkeys), in a 3-month biodistribution and toxicology pilot study and a 6-month GLP biodistribution and toxicology study.

In NHPs, which received a bilateral IVT administration of SPVN20 (7.0E+09 to 7.0E+10 vg/eye), the PK assessment included the evaluation of the shedding (by qPCR) in tears, saliva, urine, biodistribution (by qPCR) in blood (toxicokinetic, TK) and in an extensive list of tissues (3 and 6-month after injection), along with the evaluation of *GIRK1(F137S)* mRNA expression (by RT-qPCR) in tissues with confirmed quantification of SPVN20 vector genome.

Only data considered relevant for the environmental risk assessment (i.e., shedding assessed by qPCR) are presented in this section.

SPVN20 DNA shedding in tears was minimal and transient in the NHP 3-month pilot study (SPVN20 DNA was quantified in only one animal over 3 tested and only on Day 3) while not detected in the tears, urine and saliva from the 6-month GLP study at both doses and at any of the tested timepoints up to Day 84.

Please refer to the confidential CAF for details on specificity and sensitivity of the method used to detect viral shedding.

SECTION 3 –INFORMATION RELATING TO THE CLINICAL TRIAL

3.1. General information about the clinical trial.

EudraCT-number (where available):	2025-520665-47
Deliberate release reference number (where available and applicable):	Not available
Title of the clinical trial:	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.
Name of principal investigator:	Dr. Emma Duignan
Objective of the study:	The primary objective is to assess the safety and tolerability of a single intravitreal injection (IVT) of SPVN20 in subjects with no light perception (NLP) due to end-stage rod-cone dystrophy (RCD), over six months after IVT. The secondary objectives are: 1- To evaluate the systemic immune response against the viral vector of SPVN20, over five years after IVT 2- To evaluate the viral shedding and biodissemination of SPVN20 genome up to one year after IVT 3- To evaluate the cardiac and neurological activities six months after IVT 4- To evaluate the preliminary efficacy following a single IVT of SPVN20 in subjects with NLP due to end-stage RCD, over five years after IVT 5- To evaluate the quality of life (QoL) following a single IVT of SPVN20 in subjects with NLP due to end-stage RCD, over five years after IVT
Intended start and end date:	In EU, the clinical trial is intended to start in July 2025 and to end in July 2031.
Number of trial subjects that will take part in the study:	The study will consist of three sequentially recruited cohorts of three subjects each treated with SPVN20, for a planned total of 9 patients.
Indicate if an application related to the same investigational medicinal	The clinical trial application was approved in Belgium on 27th of May 2025 and was submitted on 06th of June 2025 in the following EU countries: France, and Republic of Ireland.

product has been submitted -or is planned to be submitted- to other EEA Member States. In the affirmative, identify the countries concerned:	

3.2. Intended location(s) of the study.

The applicant should provide information about the sites located in the country of submission of the application.

In some jurisdictions, the following additional information should be provided:

- *the location(s) of laboratories (in the country of submission) in which activities with the GMO are carried out under the framework of the clinical trial application should be stated.*[7]
- *information about the location where the investigational medicinal product is stored (to the extent that the location is in the country of submission but outside the clinical site).*[8]
- *information about the location where patient's samples that contain GMO's are stored (to the extent that the location is in the country of submission but outside the clinical site).*[9]

Organisation Name:	Royal Victoria Eye and Ear Hospital
Address Details:	Adelaide Road, Dublin 2, Ireland
Contact person:	Dr. Emma Duignan
Telephone No:	0035316644600
Email Address:	emma.duignan@rveeh.ie
Planned activities:	Storage and handling of SPVN20 at the clinical site Administration of SPVN20 to study subjects Follow-up of study subjects (including biological samples collection) Patient samples storage at the site
Containment level:	**Level 2**
Name and contact details of	**Ireland** Dr. Emma Duignan emma.duignan@rveeh.ie

[7] Information about the location of laboratories is required for applications submitted to Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Portugal and Spain. In case of submissions to these jurisdictions, fill in the relevant table for laboratories that conduct specialised analysis referred in the protocol of the clinical trial only; laboratories that perform standard laboratory diagnostics analysis need not be listed.
[8] This information should be provided for applications submitted to Croatia, Germany, Ireland and Spain. This information should be provided for applications submitted to Belgium, Czech Republic and Finland, unless there is a contained use notification covering the storage of the product.
[9] This information should be provided for applications submitted to Germany and Ireland.

the responsible person:	

(Applicant should complete as many tables as necessary)

3.3. Storage of the clinical vector at the clinical site.

The applicant should provide information about the storage location, conditions of storage (including restrictions of access), and the maximal storage duration.[10]

The IMP will be prepared in the hospital's pharmacy in a pharmacy clean room (Grade C environment, grade A positive pressure isolation) dedicated to contained use. More details are provided in Section 4.1. SPVN20 is supplied as part of a patient kit which includes one vial of SPVN20 Drug Product, two diluent vials, an empty 2 mL vial and an empty 10 mL vial. Instruction for reception, storage and preparation of the dose to be injected to a patient are given in the Pharmacy Manual (in Section 5.). The patient kit is to remain stored in its secondary container at the hospital's pharmacy, in a secure area with restrictive access, inside a controlled freezer (≤ -60°C) with alarm functionality, until the time of thawing. The freezer temperature log should be kept in the study file and made available for monitoring purposes. The maximal storage duration of SPVN20 at the clinical site will be until the end of the recruitment period of the study. SPVN20 Drug Product shelf-lives are communicated to the clinical site and Principal Investigator on a rolling-basis, in the relevant study documents (e.g., Investigator's Brochure).

3.4. Logistics for on-site transportation of the clinical vector.

The applicant should provide information about the logistics for in-house transportation (i.e. transfer of the clinical vector from storage to the administration site and –where applicable- site where dose is prepared). The applicant should provide information about the characteristics of the containers used addressing also disinfection procedures applied and labelling of the containers.

The dilution steps should be performed at the hospital's pharmacy using a sterile technique under aseptic conditions in a Class A positive pressure isolation room, and at room temperature. Once dilution steps are completed at the hospital's pharmacy, the filled injection syringe containing "Final diluted SPVN20 Drug Product" will be placed in a sterile, leak proof, sealed bag. The sealed bag will be placed into an appropriate closed container (e.g., hard-plastic cooler or box) for transportation to the treatment room, according to the standard hospital procedures. On the outside a biohazard symbol is placed on the container. Only trained staff members are allowed to transport the GMO.

3.5. Information about reconstitution, finished medicinal product and administration to patients.

Reconstitution (where applicable, summarise reconstitution steps):	No reconstitution. Dilution of the SPVN20 Drug Product will be performed per Pharmacy Manual instructions and local biosafety guidelines at the hospital's pharmacy. Dedicated final

[10] In case of applications submitted to Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Ireland, Italy, the Netherlands and Spain, the applicant should specify if the dose is being prepared in the hospital pharmacy. If the clinical dose is prepared at a location other than the hospital pharmacy, this should be explained.

	formulation buffer (SPVN Diluent) will be used for the dilution.
Pharmaceutical form and strength:	Sterile suspension (supplied to the clinical site as a frozen product ≤-60°C). The SPVN20 DP vial contains a nominal volume of 0.3 mL at a concentration of 4.5E+12 vg/mL in FFB comprised of sterile Balanced Saline Solution (BSS) at pH 7.2, supplemented with 0.001% Poloxamer P 188®.
Mode of administration:	Intravitreal injection
Information on dosing and administration schedule (in case of repeated dosing):	One single intravitreal administration of SPVN20 in the worse-seeing eye. No repeated dosing allowed
Information on concomitant medication that may affect the shedding of the clinical vector/ environmental risks (*e.g.* administration of laxatives, administration of a medicinal product that could enhance the replication activity of the clinical vector, administration of a plasmid-based medicinal product):	Any immunosuppressive therapies, other than the immunomodulatory corticosteroids-based regimen required in the protocol are prohibited. However, study centers are to follow their standard procedures in case of adverse event or medical emergency requiring immunosuppressive therapy.

3.6 Measures to prevent dissemination into the environment.

a) Control measures during reconstitution (if applicable), handling and administration.

The control measures during reconstitution, handling and administration are as follows:
The Drug Product is to remain stored in its secondary container at the investigational site, in a secure area at the hospital pharmacy with restrictive access, inside a controlled freezer (≤ -60°C), until the time of thawing. The freezer temperature log should be kept in the study file and made available for monitoring purposes.
Once out of the freezer, all further steps should be conducted at room temperature, under aseptic conditions in a Class A positive pressure isolation room.
The vials must be inspected for damage and particulates before dilution.
Before dilution, the vials contained in the patient kit should be decontaminated using appropriate cleaning agent per standard hospital procedures.
For doses requiring serial dilution, the “Intermediate Diluted SPVN20” should be removed and discarded in an appropriate biohazard container prior to filling the administration syringe with the “Final Diluted SPVN20”, to avoid any mix-up.
The needles and syringes used for dilution steps should be disposed in an appropriate biohazard container.
The BSC should be resanitized after preparation of the “Final Diluted SPVN20” and prior to the preparation of the administration syringe.
The two injection syringes each containing 0.2 mL of “Final Diluted SPVN20” should be placed in an aseptic manner into a sterile plastic bag, and the bag sealed.

The sterile plastic bag containing the 2 filled injection syringes should be placed into an appropriate secondary container (e.g., hard-plastic cooler or box) for delivery to the surgical suite at room temperature.
The intravitreal injection administration should be performed by an experienced ophthalmologist in a treatment room. Ideally, the room is dedicated to intraocular injections or other sterile interventions. The room should be cleaned before being used to the same standard as an operating theater.

b) Personal protective equipment.

Medical personnel will follow standard hospital hygienic measures, standard hospital personal protective equipment will be worn, such as coats and gloves.

c) Decontamination/cleaning measures after administration or in the case of accidental spilling (*i.e.* decontamination /cleaning measures of potentially contaminated materials, surfaces and areas). In addition, the disinfection procedures applied should be justified by providing evidence that the chosen method is sufficiently active against the clinical vector.

A major spill is a potentially serious incident, even if there is no obvious accidental exposure. Examples may include breakage of a sample container and/ or spillage of whole vials – rather than just a minor splash during manipulation.
All non-essential personnel will leave the contaminated area. Staff attending the incident will wear protective clothing appropriate to the class of spilled agent (disposable gown, apron, gloves - available in the spillage kit) and goggles for eye protection. Get the spillage kit and pour sufficient disinfectant onto the spill. Suitable disinfectants include Mediclean 1,000 ppm chlorine, or 6% hydrogen peroxide. For AAV decontamination, the use of 0.5% sodium hypochlorite during a minimum of 10 min of contact time is a validated procedure.
Leave for 5 minutes. Longer exposure does not increase hygiene whilst risking damaging surfaces. Use absorbent cloth/pad to absorb all the liquid. Thoroughly wash the area using water. Do not use other disinfectants or alcohol, as it is likely to cause frothing or smearing which may be difficult to remove. Dry area using absorbent cloth, e.g. paper towels. All waste from the spillage should be treated as appropriate for that Class in line with the waste disposal procedure.

d) Elimination or inactivation of left-overs of the finished product at the end of the clinical trial.

Any unused patient kit will be returned to the Sponsor upon request, or at the end of the clinical trial. Destruction of unused patient kits is the responsibility of the Sponsor.
Left-overs of the finished product, personal protective equipment (e.g. gloves etc.) and any other components that have been in contact with the product before and during administration will be disposed of per local biosafety guidelines according to standard hospital procedures. All single use equipment will be removed in medical waste (RMA) containers according to the waste management plan.

e) Waste treatment (including also –where applicable- decontamination and disposal of potentially contaminated waste that accumulates outside the clinical trial site). Where applicable, identify also the company responsible for waste management.

GMO waste which has not been inactivated needs to go into black lidded containers for export. All autoclaved waste can be placed in a yellow lid rigid container/30.2 Bio system container for disposal A registered waste transporter collects the hazardous medical waste 3 times a week from the campus for incineration at Stericycle.

f) Recommendations given to clinical trial subjects to prevent dissemination (where applicable).

Patients are brought into a single room, with daily cleaning as well as thorough cleaning at patient discharge. Considering the low volume of IMP, as well as the administration route of an intravitreal injection, the dissemination risk is considered minimal.

g) Recommendations on donation of blood/cells/tissues/organs by the clinical trial subject.

The Sponsor recommends avoiding donation of sperm, ovocytes, blood, tissue, cell or organs for any subjects for 1 year following the administration of SPVN20. After this period, the decision is left to the subject, in consultation with the investigator and/or primary care provider, as appropriate.

(i) Other measures (where applicable).

Based on the risk assessment, no other measures are foreseen.

3.7. Sampling and further analyses of samples from study subjects

This Section should be filled in where samples are being taken from patients which may contain GMOs in the context of the clinical trial and the application is submitted to the following jurisdictions: Croatia, Czech Republic, Germany, Ireland, the Netherlands, Spain

a) Describe how samples will be handled/stored/transported.

To the extent that handling/ storage and transport of samples are treated under same procedures as the clinical vector, cross-reference can be made as appropriate.

Patient samples for laboratory safety assessment (hematology, chemistry, urinalysis) will be collected and analyzed as per standard hospital procedures. Patient sampling for biodistribution (i.e., blood), shedding (i.e., tears and urine) and for immunological (i.e., serum and blood for PBMC processing) assessments will be performed within the treatment room and all samples will be labelled, handled, stored and shipped as per instructions given by the Sponsor in the 'Central Laboratory Manual'. Samples for biodistribution (i.e., blood), shedding (i.e., tears and urine) and for immunological (i.e., serum) assessments will be sent frozen to the Central Laboratory for centralization and then be shipped to third parties for analysis. The frozen samples will be sent to the Central Laboratory after completion of Visit 6 or upon Sponsor's request via a premium courier. On the requested day of pick-up, a shipping box containing dry-ice and properly labeled with UN3373 sticker for Biological Substance Category B will be provided by the courier. Blood samples for PBMC processing (for immunological assessment) by the Central Laboratory will be sent at room temperature on day of sampling due to the stability period of the samples. For the shipment at room temperature, all the labeled tubes will be placed in an absorbent sleeve (1 tube per slot) and the sleeve placed in a 95kPA bag. The bag will be closed by removing the white strip and inserted into a white box labeled with UN3373 sticker for

Biological Substance Category B. The box will be placed into the courier flyer and sealed and a signed airwaybill placed in the plastic pouch of the courier flyer.

b) Indicate whether and at which time points samples that may contain the administered clinical vector are taken from study subjects.

Blood (for laboratory safety assessment), serum and blood for PBMC processing (for evaluation of the immunological response) will be collected at various timepoints until the end of the study (Year 5 or Early Termination). Tears and urine will be collected to evaluate the vector shedding and whole blood to evaluate the vector biodissemination at all visits until Year 1 (included). For those samples, analysis will be performed until results of three consecutives timepoints are below the limit of detection of the assay.

c) If samples are stored at the clinical site, describe storage location and storage conditions.

Following examination, samples for laboratory safety assessments (blood) are stored at the hospital at optimum temperature for specified times. These times conform with Department policy outlined in the Control of Clinical Material procedure, MP-GEN-CLINMCON. Samples for vector shedding, biodissemination and evaluation of the immunological response will be stored frozen at the clinical site as per instructions given by the Sponsor in the 'Central Laboratory Manual' until their centralization to the Clinical Laboratory and shipment to third parties for analysis. Primary and back-up samples from the same patient and same visit should always be stored in separated area. Furthermore, storage of research samples will be separate from diagnostic samples.

d) Explain if there is any non-routine[11] testing of the samples and indicate whether the clinical vector is generated *de novo* during the testing.

Not applicable.

SECTION 4 – OTHER DATA REQUIREMENTS

4.1. Plan of the site(s) concerned

Applicants should provide a copy of the plan of the site where the clinical trial takes place if the application is submitted to the following jurisdictions: Austria, Belgium, Croatia, Czech Republic, Finland, France, Hungary, Ireland and Italy.

Please refer to the confidential CAF for details.

[11] Standard clinical care tests as well as tests required to fulfil long-term follow-up of clinical trial subjects need not be mentioned.

4.2 Other information

Submissions to Austria:

In addition to the plan of the site, a description of the location of the autoclave should be provided – as appropriate- as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).

Submissions to Belgium:

In addition to the plan of the site, a description of the location of the autoclave and the biosafety cabinet should be provided –as appropriate- as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).

The applicant is also asked to provide an overview (table) of the rooms involved in the CT activity by indicating for each of those the number of the room, the type of handling carried out (e.g. storage, administration of the IMP, reconstitution of the IMP) and the containment level.

Submissions to Czech Republic:

In addition to the plan of the site, a description of the location of the autoclave should be provided – as appropriate- as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).

Submissions to Denmark:

- *The applicant should explain if left-overs are stored at the clinical site and, if in the affirmative, for how long as part of the information submitted in Section 3(6)(d).*
- *The applicant should provide the following information on waste treatment in Section 3(6)(e):*
  - *Whether and for how long the waste will be stored (or frequency of waste disposal),*
  - *Storage location,*
  - *Logistics for on-site transportation of the waste (similar as asked for the clinical vector in Section 3.4), and*
  - *In case of chemical decontamination whether the chosen disinfectant and method is sufficiently active against the clinical vector (similar as in Section 3.6.c)*

Submissions to France:

The plan of the site should indicate clearly the location of a PSMII, or an equivalent device.

Submissions to Germany:

- *The applicant is not required to provide further information in Section 3(6)(c) if he/she confirms that the disinfectant and decontamination procedure are included in the list of the Robert Koch Institute of currently approved disinfectants and disinfectant procedures or the VAH (Verbund für Angewandte Hygiene e.V) list of disinfectants.*
- *The applicant should explain if left-overs are stored at the clinical site and, if in the affirmative, for how long as part of the information submitted in Section 3(6)(d).*
- *The applicant should provide the following information on waste treatment in Section 3(6)(e):*

- *Whether and for how long the waste will be stored (or frequency of waste disposal),*
- *Storage location,*
- *Logistics for on-site transportation of the waste (similar as asked for the clinical vector in Section 3.4), and*
- *In case of chemical decontamination whether the chosen disinfectant and method is sufficiently active against the clinical vector (similar as in Section 3.6.c)*
- *If samples are stored at the clinical site, the maximum duration of the storage should be stated in Section 3.7 (c).*
- *The applicants is required to provide emergency response plans.*

Submissions to Ireland:

- *In addition to the plan of the site, a description of the location of the autoclave should be provided –as appropriate- as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).*
- *If samples are stored at the clinical site, the maximum duration of the storage should be stated in Section 3.7(c).*

Submissions to Italy:

- *In addition to the plan of the site, a description of the location of the autoclave should be provided –as appropriate- as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).*
- *If the manufacturer of the clinical vector is located in Italy, the authorisation issued to the premises should be declared in Section 1.3.*

SECTION 5- ENVIRONMENTAL RISK ASSESSMENT

Specific environmental risk assessment

Considering the specific characteristics of the investigational medicinal product (as described in Section 2 of the application form), the applicant considers that the specific environmental risk assessment provided for in Section 2 of the Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors is applicable:

Yes ☒

No ☐

If the answer to the above is NO, the following information should be provided:

- *For submissions made under Directive 2001/18/EC*: an environmental risk assessment is required in accordance with Annex II thereof.
- *For submissions made under Directive 2009/41/EC*: an assessment of the risks to human health and the environment in accordance with Article 4 thereof.

If applicable – ANNEX (Confidential information)

ATTACHED DOCUMENTS

☐ Description biological materials
☐ Biosafety plans of the rooms involved in the activity (section 4.1)
☒ Containment measures, working practices and personal protective equipment
Appendix 1 – Policy and Procedure for Personal Protective Equipment
Appendix 2 – Medication Incident Reporting
Appendix 3 – Environmental and Physical Monitoring of Isolator and Cleanroom
Appendix 4 – Policy and Procedure for handling ATMP Gene Therapy Medicinal Products
Appendix 1 – 4 are considered confidential to the hospital, therefore not for general distribution; Please refer to the confidential CAF for details.
☐ Prevention of incidents
☐ Advice of the biosafety committee
☐ Confidential information as extra file
☐ Other attachments: