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, Luxembourg, the Netherlands, Portugal, Romania, 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)

[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, Luxembourg, the Netherlands, Portugal, Romania, 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:

[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).

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 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:	Syneos Health Branches Limited
Address Details:	Farnborough Business Park, 1 Pinehurst Road, Farnborough, Hampshire, GU14 7BF, United Kingdom
Contact person:	Holly Jacobs
Telephone No:	+44 737 843 0737
Email Address:	holly.jacobs@syneoshealth.com

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

Organisation Name:	MeiraGTx UK II Limited
Address Details:	92 Britannia Walk London, N1 7NQ, United Kingdom (UK)
Contact person:	Robert Zeldin
Telephone No:	
Email Address:	robert.zeldin@meiragtx.com

1.3 Identification of the manufacturer of the clinical vector.

Organisation Name:	MeiraGTx UK II Limited
Manufacturing location:	92 Britannia Walk London, N1 7NQ, United Kingdom (UK)

SECTION 2 INFORMATION RELATING TO THE INVESTIGATIONAL MEDICINAL PRODUCT

2.1 Description of the production system.

Clear maps of the vectors used for rcAAV 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.

AAV5-hRKp.RPGR (INN: botaretigene sparoparvovec) is a gene therapy product derived from a recombinant, replication-incompetent, adeno-associated virus (AAV) viral vector with a serotype 5 capsid (AAV5). As with other recombinant AAV (rAAV) vectors, AAV5-hRKp.RPGR has a compact macromolecular structure and forms stable viral particles approximately 25 nm in diameter. AAV5-hRKp.RPGR incorporates the following key elements:

- An expression cassette flanked by the wild-type (WT) AAV serotype 2 (AAV2) inverted terminal repeats (ITRs) that provide the packaging signal, packaged in an AAV5 capsid
- A human rhodopsin kinase promoter (*hRKp*), that drives cell specific gene expression in rod and cone photoreceptors
- A polyadenylation signal that enhances gene expression
- A complementary deoxyribonucleic acid (cDNA) encoding a shortened form of the human retinitis pigmentosa guanosine triphosphatase regulator open reading frame 15 (*hRPGR.ORF15*).

AAV5-hRKp.RPGR is currently being developed as a gene therapy product for patients with X-linked retinitis pigmentosa (XLRP) caused by mutations in the human retinitis pigmentosa guanosine triphosphatase regulator (RPGR) gene. AAV5-hRKp.RPGR is administered to the subretinal space following a standard surgical vitrectomy.

AAV5-hRKp.RPGR is manufactured using transient transfection of the HEK293 cell line with a triple plasmid mixture namely, RPGR transgene plasmid, helper plasmid and packaging plasmid. AAV5-hRKp.RPGR is then purified using a multi-step downstream process. The drug substance, drug product and manufacturing process are monitored with an extensive panel of quality control tests and appropriate test methods are in place for drug product release. Key testing includes transgene identity, capsid identity, total vector genome titer, percentage of full capsids, purity and protein identification, infectious titer, *in vivo* potency as well as replication-competent AAV (rcAAV).

The HEK293 cell line was derived from human embryonic kidney cells transfected with fragments of mechanically sheared human adenovirus type 5 DNA and selected for characteristics of adenoviral transformation with early region 1 genes (E1A and E1B) (Graham et al., 1977). The fully characterised master cell bank used for the production of AAV5-hRKp.RPGR has been extensively tested for potential

non-viral and viral adventitious agents (further details are considered confidential and are described in Annex 1).

Genetic material and potential interactions with the clinical vector are discussed in confidential Annex 1.

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.

AAV5-hRKp.RPGR is a recombinant AAV vector in which the wild-type AAV rep and cap genes are replaced by the RPGR expression cassette. Thus, AAV5-hRKp.RPGR is unable to replicate independently, even in the presence of a helper virus.

Risk of generation of rcAAV as a result of recombination events occurring during the manufacturing process

The probability of a replication event during manufacture is low since AAV5-hRKp.RPGR is manufactured with all the genetic elements provided in trans and furthermore uses helper plasmid rather than co-infection with helper virus, and there is no transferred wild-type adenovirus in the drug substance manufacturing.

The presence of rcAAV is tested on each batch of drug product by a validated cell-based assay using quantitative polymerase chain reaction (PCR). Test methods for detection of replication-competent virus and release criteria with regard to rcAAV testing of AAV5-hRKp.RPGR batches are considered confidential and provided in Annex 2.

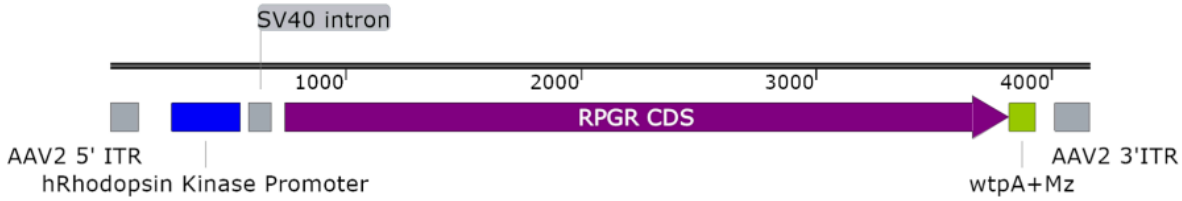
Risk of generation of rcAAV as a result of recombination events occurring in patients after administration.

The generation of rcAAV in patients after administration of AAV5-hRKp.RPGR would only be possible in the extremely unlikely event of triple infection of the same host cell by AAV5-hRKp.RPGR, wild-type AAV and helper viruses such as adenovirus or herpes simplex virus. However, such recombination event could only result in the exchange of the transgene expression cassette with the rep and cap genes of the wild-type AAV as it is not possible for the AAV genome to contain both rep and cap genes and the transgene expression cassette, due to the limited packaging capacity of AAVs. Moreover, the regions of homology between AAV5-hRKp.RPGR and a potential co-infecting wild-type AAV would be limited to the ITRs, since the rep and cap genes are not present in AAV5-hRKp.RPGR. This further decreases the possibility of recombination leading to rcAAV. See Section 2.4 for further details on possible recombinants and discussion of their biological significance.

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

AAV5-hRKp.RPGR is a recombinant AAV vector that incorporates the following features:

- An expression cassette flanked by the WT AAV serotype 2 (AAV2) ITRs that provide the packaging signal, packaged in an AAV5 capsid
- A human rhodopsin kinase promoter (*hRKp*), that drives cell specific gene expression in rod and cone photoreceptors
- An SV40 intron upstream of the therapeutic gene that enhances expression of the therapeutic gene
- A polyadenylation signal that enhances gene expression
- A complementary deoxyribonucleic acid (cDNA) encoding a shortened form of the human RPGR open reading frame 15 (*hRPGR.ORF15*)



AAV: adeno-associated virus; ITR: inverted terminal repeat; RPGR CDS: human retinitis pigmentosa GTPase regulator coding sequence; wtpA+Mz PolyA: Polyadenylation sequence

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.

The nucleotide sequence of AAV5-hRKp.RPGR and the exact location of each of the sequence features are considered confidential information, please refer to Annex 3 for details.

Deviation of clinical vector from parental virus

The AAV5-hRKp.RPGR viral genome has been significantly modified compared to the parental virus in order to render it replication incompetent. The AAV rep and cap genes have been replaced with a eukaryotic expression cassette. The only viral elements are the ITR sequences derived from AAV2, which are non-coding DNA sequences. The ITRs have been retained because they are required to enable replication and packaging of the vector genomes during manufacturing as well as for second-strand synthesis in transduced cells.

A detailed description of the expression cassette is provided in Section 2.5.

Genetic stability:

Evolution of AAV viruses (like all viruses) is directed by spontaneous mutations or recombination with other viruses of the same species, when such genetic modification confers a selective advantage. Non-homologous genomic recombination may occur spontaneously in nature between the viral genomes of AAV strains only under circumstances where a cell of the host organism is infected simultaneously by two different strains of AAV, which is permissive in that species (permissive cell line providing helper functions or presence of a helper virus).

AAV5-hRKp.RPGR is expected to be highly genetically stable. AAV5-hRKp.RPGR is generated by transient transfection of HEK293 cells using fully characterised, sequenced plasmids (see Section 2.1 and Annex 1). Production of the vector in the manufacturing process and second-strand synthesis of the vector genome rely on the host DNA polymerase, characterised by high fidelity DNA polymerisation and additional proofreading exonuclease activity, leading to very low error rate of DNA replication.

The genomic integrity of the AAV5-hRKp.RPGR vector genome is tested on drug substance. DNA sequencing of the vector genome is conducted on the packaged expression cassette (ITR to ITR) using Next Generation Sequencing. Furthermore, the drug substance and drug product are characterised by a comprehensive panel of in process controls and release tests ensuring critical quality attributes meet the acceptance criteria. Please refer to Annex 3 for details on the analytical methods used to test AAV5-hRKp.RPGR.

AAV5-hRKp.RPGR is unable to replicate independently, even in the presence of a helper virus such as adenovirus, since it lacks the rep and cap genes required for replication and packaging, respectively. AAV5-hRKp.RPGR replication could only occur in the extremely unlikely event of a triple infection of the same host cell by AAV5-hRKp.RPGR, wild-type AAV (providing the rep and cap functions) and a helper virus. The triple infection event could result in the recombination of the AAV5-hRKp.RPGR expression cassette with the rep and/or cap genes of the wild-type virus. However, due to the limited packaging capacity of AAVs, recombination could only result in the exchange of the transgene expression cassette with the rep and cap genes of the wild-type AAV, as it is not possible for the AAV genome to contain both rep and cap genes and the transgene expression cassette.

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.

AAV5-hRKp.RPGR expression cassette includes the following elements:

- A human rhodopsin kinase promoter (*hRKp*), that drives cell specific gene expression in rod and cone photoreceptors
- An SV40 intron upstream of the therapeutic gene that enhances expression of the therapeutic gene
- A polyadenylation signal that enhances gene expression
- A complementary deoxyribonucleic acid (cDNA) encoding a shortened form of the human RPGR open reading frame 15 (*hRPGR.ORF15*) (details on the shortened form are provided in Annex 4)

The function of each constituent part of expression cassette is known as detailed above and no potentially harmful sequences are encoded in AAV5-hRKp.RPGR.

AAV5-hRKp.RPGR is administered to the subretinal space to deliver a functional transgene encoding the *hRPGR* gene to the target tissue to provide functional RPGR protein facilitating functional and morphological rescue of photoreceptors and consequently improving vision. The RPGR protein is a non-toxic protein which is expected to be metabolised naturally and in the same manner as endogenous human RPGR. In non-clinical toxicology studies, subretinal administration of AAV5-hRKp.RPGR did not result in underlying illness, change of behaviour or local adverse effects on retinal structure or function.

AAV5-hRKp.RPGR is a replication-incompetent virus and is therefore at a competitive disadvantage when compared to WT AAV strains. The RPGR transgene is not expected to confer any advantage to the GMO in terms of survival and selective pressure.

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.

Non-clinical biodistribution and shedding

The biodistribution of AAV5-hRKp.RPGR in tissues and the shedding of AAV5-hRKp.RPGR in blood after a single dose of vector administered by subretinal injection (bilateral) have been assessed in WT mice and New Zealand White rabbits at two different doses and assessed by quantitative real-time PCR.

In mice, some dissemination of vector to the liver, kidney, brain, lungs and adrenal glands was detected with the highest number of detected genome copies in the liver. 'Low dose' animals at day 7 showed relatively low numbers of vector genomes in the tissues that were positive at high dose, with the exception of the liver. At day 28, a general decrease in vector genomes was observed and complete absence at day 56. Blood samples obtained from animals in all groups on day 7 were negative for the presence of vector genomes; samples obtained at later time points were not analysed.

In rabbits, mainly low-level dissemination of vector to the optic tract, liver and spleen was detected. The highest genome copy numbers were found in the optic nerve of the injected eye. Although no vector was detected in serum at day 7, the presence of vector genomes in the liver and spleen would suggest that there was some release of vector into the bloodstream, most likely during surgery and potentially aggravated by the trans-choroidal route of administration. The absence of vector genomes in other major organs is explained by the natural tropism of AAV vectors to the liver. Low levels of genomes were found in the liver and superior colliculus at both 28 days and 56 days. Assessment of 'low dose' animals showed sporadic presence of low numbers of vector genomes in the liver, superior colliculus, the optic nerve head of the injected eye, the retinal pigment epithelium and optic nerve head of the uninjected eye. No genomes were found in any tissues in vehicle treated animals at day 7.

Further details on the non-clinical studies are provided in Annex 5.

Clinical biodistribution and shedding

To date there have been no completed clinical studies of AAV5-hRKp.RPGR in humans. In study MGT009 (Phase I/II, open-label, dose-escalation clinical study with three dose levels to investigate the safety and potential efficacy of subretinally administered AAV5-hRKp.RPGR in participants aged 5 years or older with XLRP caused by mutations in RPGR, EudraCT 2016-003967-21), data on biodistribution and viral shedding are being collected.

In the planned clinical Phase III study (EudraCT 2020-002873-88), lacrimal fluid (tear) from both eyes, saliva, whole blood, and serum samples will be collected until 4 weeks post administration of AAV5-hRKp.RPGR. These samples will be analysed by qPCR to evaluate the biodistribution and shedding of AAV5-hRKp.RPGR genome.

SECTION 3 INFORMATION RELATING TO THE CLINICAL TRIAL

3.1 General information about the clinical trial.

EudraCT-number (where available):	2020-002873-88 (MGT-RPGR-021) and 2020-002255-37 (MGT-RPGR-022)

Deliberate release reference number (where available and applicable):	N/A
Title of the clinical trial:	Phase 3 Randomised, Controlled Study of AAV5-hRKp.RPGR for the Treatment of X-linked Retinitis Pigmentosa Associated with Variants in the RPGR gene - 2020-002873-88 (MGT-RPGR-021) and Phase 3 Follow-up Study of AAV5-hRKp.RPGR for the Treatment of X-linked Retinitis Pigmentosa Associated with Variants in the RPGR gene - 2020-002255-37 (MGT-RPGR-022)
Name of principal investigator:	Professor David Keegan
Objective of the study:	The primary objective is to assess the effect of bilateral treatment with AAV5-hRKp.RPGR on retinal function as measured by static perimetry.
Intended start and end date:	December 2021 – December 2028
Number of trial subjects that will take part in the study:	A target of 51 to 60 adult participants and up to 6 paediatric participants will be enrolled in this study.
Indicate if an application related to the same investigational medicinal product has been submitted -or is planned to be submitted- to other EEA Member States. In the affirmative, identify the countries concerned:	Applications relating to the Phase 3 study of this AAV5-hRKp.RPGR are intended for submission to the following EEA countries: Belgium Denmark France Germany Ireland Italy Netherlands Spain Switzerland A Phase 1/2 first in human Study MGT009 to assess the safety, dose selection, and efficacy of the treatment in adults and children with RPGR-XLRP was initiated by MeiraGTx in 2017 (MGT009; EudraCT 2016-003967-21) and is ongoing. The study is being conducted in the UK and the US.

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:	Mater Misericordiae University Hospital
Address Details:	Eccles Street, Dublin 7, D07 R2WY, Ireland
Contact person:	Professor David Keegan
Telephone No:	+ 353 - (0)1-830-7059
Email Address:	dkeegan@mater.ie
Planned activities:	*Location where the investigational medicinal product is stored, patients treated, and where patient's samples that contain GMO's are stored before being sent to central labs outside of Ireland.*
Containment level:	Level 1
Name and contact details of the responsible person[10]**:**	Professor David Keegan Principal Investigator + 353 - (0)1-830-7059 dkeegan@mater.ie

(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.[11]

Storage will be in line accordance with national legislation.

[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.

[10] The responsible person is either the person responsible for supervision and safety as provided for under Annex V of Directive 2009/41/EC, or the responsible scientist as provided for under Annex IIIA of Directive 2001/18/EC.

[11] 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.

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.

In-house transport (i.e. at the clinical site) takes place according to local guidelines. It is recommended that transport takes place in a closed container that is easy to decontaminate, and break- and leak-proof.

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

Reconstitution (where applicable, summarise reconstitution steps):	Not applicable, no reconstitution required.
Pharmaceutical form and strength:	The drug product is supplied as a 1.2 mL sterile solution with two targeted concentrations of 2.0 x 10^{11} vg/mL and 4.0 x 10^{11} vg/mL.
Mode of administration:	Subretinal injection
Information on dosing and administration schedule (in case of repeated dosing):	AAV5-hRKp.RPGR gene therapy will be administered by subretinal injection using a standardised surgical procedure. Eligible participants in MGT-RPGR-021 will be randomly assigned to immediate bilateral treatment with the RPGR 2.0 x 10^{11} dose (in up to 800 µL in each eye), immediate bilateral treatment with the RPGR 4.0 x 10^{11} dose (in up to 800 µL in each eye), or deferred bilateral treatment. Participants in the deferred bilateral treatment group will be treated as part of Study MGT-RPGR-022 approximately 1 year after completion of all baseline examinations. All participants will be offered bilateral treatment, with the second eye treated 7 to 21 days after the first.
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):	At this stage of the drug development, there is no information on concomitant medications that may affect shedding of the clinical vector. Concomitant medication other than the required concomitant medication regimen should be avoided unless medically necessary, should be used with caution, and appropriately documented on study logs where used.

3.6 Measures to prevent dissemination into the environment.

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

Standard hospital hygienic measures will be effective during reconstitution, handling and administration of the GMO.

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.

Appropriate validated detergent and methods, suitable for AAV and according to local legislation will be used for decontamination and disinfection measures after administration of AAV or in the case of accidental spilling.

AAV is readily inactivated by several disinfectants such as 0.5% sodium hypochlorite, 0.45% potassium peroxymonosulfate (Korte et al., 2021), 0.5% peracetic acid, 10% bleach iodine and iodine (1%) (5- or 30-minute contact time; Howard and Harvey, 2017). AAV is also inactivated by autoclaving for 30 minutes at 121°C (Howard and Harvey, 2017).

AAV5-hRKp.RPGR is a non-enveloped virus and resistant to alcohol-based disinfectants (Korte et al., 2021).

References:

Howard DB, Harvey BK. Assaying the Stability and Inactivation of AAV Serotype 1 Vectors. Hum Gene Ther Methods. 2017;28(1):39-48.

Korte J, Mienert J, Hennigs JK, Körbelin J. Inactivation of Adeno-Associated Viral Vectors by Oxidant-Based Disinfectants. Hum Gene Ther. 2021;32(13-14):771-781.

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

Left-overs of the finished product will be treated according to the local laws and/or policies. Left over product, from the procedure, will be treated according to the Biosafety measures/ local laws/policies for Level 1 material.

Unused IMP stock will be returned to the Sponsor at the end of the clinical trial.

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.

All disposable waste that has been in contact with the investigational product during preparation and administration, as well as waste from sampling and sample processing, will be treated according to the local laws and/or policies.

Non-disposable materials are disinfected with appropriate disinfectants or autoclaved according to local guidelines.

The autoclave is located in the CSSD Department, Rosary House, Mater Misericordiae University Hospital, Eccles Street, Dublin 7, D07 R2WY. The Model type is the Matachana Steam Sterilisers which reaches 134

degrees centigrade. (CSSD – Central Sterile Supplies Department)

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

Based on the risk assessment, as outlined in this document, recommendations given to the clinical trial subjects to prevent dissemination, are not applicable.

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

No recommendations on donations by the clinical trial subjects are planned or considered necessary (Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors).

(i) Other measures (where applicable)

Based on the risk assessment, as outlined in this document, 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.

Standard hospital hygienic measures will be effective during sampling and handling/analyses of the samples. In-house transport takes place in a closed, easy to decontaminate, break- and leak-proof packaging. Samples will be stored in a closed container at the facility.

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

Lacrimal fluid (tear) from both eyes, saliva, whole blood, and serum samples will be collected until 4 weeks post administration of AAV5-hRKp.RPGR for analysis by qPCR to evaluate the biodistribution and shedding of AAV5-hRKp.RPGR genome.
Blood and serum samples will be taken at various time points post administration, namely on the day of administration, day 1, day 4 and weeks 4, 6, 10, 12, 26, 39 and 52 post administration.

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

Standard hospital hygienic measures will be effective during sampling and handling/analyses of the samples. In-house transport takes place in a closed, easy to decontaminate, break- and leak-proof packaging. Samples will be stored in a closed container at the facility under circumstances with restricted access.

Storage Location & Storage Conditions (Level 1)

-80 & -20 freezers are located in the Clinical Research Centre, Catherine McAuley Centre, Nelson Street, Dublin 7, D07 KX5K

24/7 temperature monitoring of all fridges and freezers with deviation alerts to protect samples is in place.

All waste material is disposed in yellow plastic bags/containers for incineration as per SOPs/local policy for level 1 contaminants.

d) Explain if there is any non-routine[12] 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.

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*

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

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 x

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.