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:	Janssen Research and Development
Address Details:	50 - 100 Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4DP
Contact person:	Cynthia Li
Telephone No:	+441494 65 8203
Email Address:	prderacta@prdgb.JNJ.com

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

Organisation Name:	Janssen-Cilag International NV
Address Details:	Turnhoutseweg 30, B-2340 Beerse, Belgium
Contact person:	
Telephone No:	
Email Address:	JCI-Office@its.jnj.com

1.3 Identification of the manufacturer of the clinical vector.

Drug Substance

Organisation Name:	Catalent Maryland Harmans (BWI)
Address Details:	7555 Harmans Road Harmans, MD21077 21201, USA

Drug Product

Organisation Name:	Catalent Maryland BioPark(BPK)
Address Details:	801 West Baltimore Street Baltimore, MD 21201, USA

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.

AAVCAGsCD59 is a gene therapy product derived from a recombinant, replication-incompetent, adeno-associated virus (AAV) viral vector with a serotype 2 capsid (AAV2). As with other recombinant AAV (rAAV) vectors, AAVCAGsCD59 has a compact macromolecular structure and forms stable viral particles approximately 20 nm in diameter. AAVCAGsCD59 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 AAV2 capsid
- The CAG promoter (CMV (cytomegalovirus) enhancer, CBA (Chicken β-actin) promoter, CBA/ RBG (Rabbit Beta Globin) chimeric intron and RBG partial exon)
- A complementary deoxyribonucleic acid (cDNA) encoding human CD59 protein truncated to delete the glycosylphosphatidylinositol (GPI) anchor.
- A polyadenylation sequence from Rabbit Beta Globin gene to terminate transcription and stabilize the mRNA transcript

AAVCAGsCD59 is currently being developed as a gene therapy product to protect host cells by inhibiting the formation of the membrane attack complex (MAC), the terminal step of complement-mediated cell lysis, in the treatment of adult patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). AAVCAGsCD59 is administered to the study eye as a single intravitreal injection.

AAVCAGsCD59 is manufactured using transient transfection of the HEK293 cells with a triple plasmid mixture namely, a transgene plasmid, adenoviral helper plasmid and AAV RepCap packaging plasmid. AAVCAGsCD59 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, vector genome titer, purity and protein identification, infectious titer, in vitro potency and ratio vector genome to infectious titer, 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 AAVCAGsCD59 has been extensively tested for potential

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

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

AAVCAGsCD59 is a recombinant AAV vector in which the wild-type AAV rep and cap genes are replaced by the hCD59 expression cassette. Thus, AAVCAGsCD59 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 generating replication competent AAV through recombination is low since an intron has been engineered into the AAV REP gene making the Rep/Cap genes on the packaging plasmid too large to package into AAV capsids. Furthemore, there are no regions of homology between the transgene plasmid containing ITRs and the RepCap genes that could facilitate homologous recombination between these plasmids.

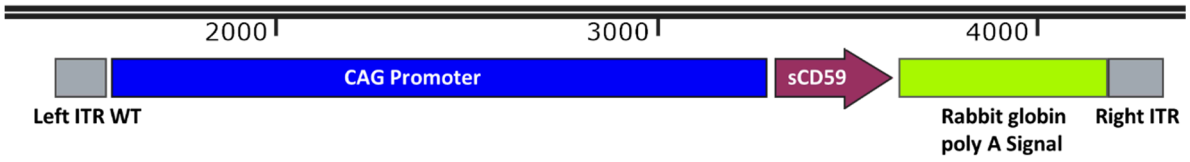
The presence of rcAAV is tested on each batch of drug product by a validated cell-based assay using quantitative polymerase chain reaction (PCR). Test methods for detection of replication-competent virus and release criteria with regard to rcAAV testing of AAVCAGsCD59 batches are considered confidential 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 AAVCAGsCD59 would only be possible in the extremely unlikely event of triple infection of the same host cell by AAVCAGsCD59, 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 AAVCAGsCD59 and a potential co-infecting wild-type AAV would be limited to the ITRs, since the *rep* and *cap* genes are not present in AAVCAGsCD59. 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.

Schematic representation of AAVCAGsCD59



ITR: inverted terminal repeat; CAG promoter: CMV (cytomegalovirus) enhancer, CBA (chimeric β-actin) promoter and CBA intron; sCD59: truncated human sCD59 cDNA, encoding a soluble CD59 protein; Poly A: Polyadenylation

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 AAVCAGsCD59 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 AAVCAGsCD59 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).

AAVCAGsCD59 is expected to be highly genetically stable. AAVCAGsCD59 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 AAVCAGsCD59 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 AAVCAGsCD59.

AAVCAGsCD59 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. AAVCAGsCD59 replication could only occur in the extremely unlikely event of a triple infection of the same host cell by AAVCAGsCD59, wild-type AAV (providing the *rep* and *cap* functions) and a helper virus. The triple infection event could result in the recombination of the AAVCAGsCD59 expression cassette with the *rep* and/or *cap* genes of the wild-type virus.

See section 2.2 for Risk of generation of rcAAV as a result of recombination events occurring during the

manufacturing process

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.

AAVCAGsCD59 expression cassette includes the following elements:

- The CAG promoter (CMV (cytomegalovirus) enhancer, CBA (Chicken β-actin) promoter, CBA/ RBG (Rabbit Beta Globin) chimeric intron and RBG partial exon)
- A complementary deoxyribonucleic acid (cDNA) encoding human CD59 protein truncated to delete the glycosylphosphatidylinositol (GPI) anchor.
- A polyadenylation sequence from Rabbit Beta Globin gene to terminate transcription and stabilize the mRNA transcript

The function of each constituent part of expression cassette is known as detailed above and no potentially harmful sequences are encoded in AAVCAGsCD59.

AAVCAGsCD59 is administered to the eye via intravitreal injection to deliver a functional transgene to the target tissue to provide functional sCD59 protein protecting host cells by inhibiting the formation of the MAC, the terminal step of complement-mediated cell lysis. The CD59 protein is a non-toxic protein which is expected to be metabolised naturally and in the same manner as endogenous human CD59. In non-clinical toxicology studies, administration of AAVCAGsCD59 did not result in underlying illness, change of behaviour or local adverse effects on eye structure or function.

AAVCAGsCD59 is a replication-incompetent virus and is therefore at a competitive disadvantage when compared to WT AAV strains. The sCD59 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

The biodistribution of AAVCAGsCD59 in tissues and the shedding of AAVCAGsCD59 in blood after a single dose intravitreal (IVT) administration of vector have been assessed in WT mice and NHPs. In the 6-month mouse study, the biodistribution of AAVCAGsCD59 was evaluated at 2 dose levels at Day 28, Day 91, or Day 182 following a single unilateral dose via IVT injection to mice. AAVCAGsCD59 DNA was detected via quantitative polymerase chain reaction (qPCR) and detected in the treated eye with the highest values seen on Day 28 and reducing quantities by Day 182. Levels of AAVCAGsCD59 DNA in other tissues were low or undetectable (See Annex 4 for details and results).

In the 6-month NHP study, the biodistribution of AAVCAGsCD59 was evaluated at 2 dose levels following a single bilateral dose via IVT injection to male cynomolgus monkeys. Animals were monitored for a 6-month postdose observation period. The presence of AAVCAGsCD59 DNA and sCD59 mRNA was confirmed in the vitreous humor and retina from treated animals at both dose levels. AAVCAGsCD59 DNA was also detected in some other tissues at lower levels (See Annex 4 for details and results).

Clinical biodistribution

In a Phase 1 AAVCAGsCD59 dose escalation study, blood was tested for the presence of AAVCAGsCD59 DNA in the 17 participants. Four from the high dose cohort had detectable levels in serum. Two participants had quantifiable levels at Day 7 that decreased below the lower limit of quantification (LLOQ) by Week 4. One participant had quantifiable levels at Week 4 that were undetectable by Week 12. One subject had detectable levels below the LLOQ at Day 7.

Published shedding data for AAV-mediated gene therapy in humans
Biodistribution studies suggest that following subretinal injection of rAAV, anterograde and transsynaptic transport of small amounts of vector genome from the retina to central visual structures may occur (Stieger et al, 2008). This is considered most likely to result from off-target transduction of retinal ganglion cells following reflux of vector suspension into the vitreous. Since only tiny amounts of vector are likely to reach the brain and a cone photoreceptor-specific promoter will be used, the possibility of transgene expression causing toxicity in the brain is considered to be highly unlikely.

In the open label, dose escalation Phase 1/2 study of AAV2/2hRPE65 (Bainbridge et al, 2008, Bainbridge et al, 2015), in 3 of 12 participants there was dissemination of vector into tears at Day 1 but not Day 30 after administration. There was no dissemination of vector into serum or saliva collected 1 day and 30 days after administration of the vector, or in semen collected at 30 days (N = 12).

In the open-label, dose-escalation Phase 1 study of rAAV-hRPE65 (Cideciyan et al, 2008; Cideciyan et al, 2009; Hauswirth et al, 2008; Jacobson et al, 2012), for all patients at all time points, there were no vector genome copies detected in peripheral blood.

In the Phase 1 dose-escalation study of AAV2-hRPE65v2 (Maguire et al, 2009), the vector was found in samples of tears and blood only transiently after subretinal injection in 6 patients with retinitis pigmentosa caused by a MERTK mutation (Ghazi et al, 2016). In both these studies, no vector genomes were detected in blood samples.

In previous clinical studies of AAV2 vectors administered in the retina, shedding of vector could be detected in tears (Boye et al, 2012) and serum samples (Manno et al, 2006), which were transiently positive, but this resolved within a few days after the operation. In a Phase 1 study, an AAV vector expressing a mitochondrial gene was administered intra-vitreally in 5 patients with Leber hereditary optic neuropathy (Feuer et al, 2016). In another Phase 1 study, an AAV2 vector expressing human MER Proto-Oncogene, Tyrosine Kinase (MERTK) was administered by subretinal injection in 6 patients with retinitis pigmentosa caused by a MERTK mutation (Ghazi et al, 2016). In both these studies, no vector genomes were detected in blood samples.

Systemic intravascular administration of rAAV2 to deliver factor IX to patients with haemophilia B can lead to vector sequences detectable in semen samples, though not sperm, for a short period (Manno et al, 2006). In that study, the presence of AAV2/2 genomes was reported in semen samples after intravenous administration of a total of ~10^{14} vg in trial subjects. Shedding of vector in the semen was detected for 2-weeks after administration in three participants and for up to 10-weeks in 1 participant; no vector genomes were detectable in semen from Week 12 onwards.

References

Bainbridge JW, Mehat MS, Sundaram V, et al. Long-term effect of gene therapy on Leber's congenital amaurosis. N Engl J Med. 2015;372(20):1887-1897

Bainbridge JW, Smith AJ, Barker SS, et al. Effect of gene therapy on visual function in Leber's congenital amaurosis. N Engl J Med. 2008;358(21):2231-2239.

Boye SE, Alexander JJ, Boye SL, et al. The human rhodopsin kinase promoter in an AAV5 vector confers rod- and cone-specific expression in the primate retina. Hum Gene Ther. 2012;23(10):1101–1115.

Cideciyan AV, Aleman TS, Boye SL, et al. Human gene therapy for RPE65 isomerase deficiency activates the retinoid cycle of vision but with slow rod kinetics. Proc Natl Acad Sci U S A. 2008;105(39):15112-15117.

Cideciyan AV, Hauswirth WW, Aleman TS, et al. Vision 1 year after gene therapy for Leber's congenital amaurosis. N Engl J Med. 2009;361(7):725-727.

Feuer WJ, Schiffman JC1, Davis JL, et al. Gene therapy for leber hereditary optic neuropathy: Initial results. Ophthalmology. 2016;123(3):558–570.

Ghazi NG, Abboud EB, Nowilaty SR, et al. Treatment of retinitis pigmentosa due to MERTK mutations by ocular subretinal injection of adeno-associated virus gene vector: results of a phase I trial. Hum Genet. 2016;135(3):327–343.

Jacobson SG, Acland GM, Aguirre GD, et al. Safety of recombinant adeno-associated virus type 2-RPE65 vector delivered by ocular subretinal injection. Mol Ther. 2006a;13(6):1074–1084.

Hauswirth WW, Aleman TS, Kaushal S, et al. Treatment of Leber Congenital Amaurosis due to RPE65 mutations by ocular subretinal injection of adeno-associated virus gene vector: short term results of a Phase I trial. Hum Gene Ther. 2008;19(10):979–990.

Maguire AM, Simonelli F, Pierce EA, et al. Safety and efficacy of gene transfer for Leber's congenital amaurosis. N Engl J Med. 2008;358:2240–2248.

Manno CS, Pierce GF, Arruda VR, et al. Successful transduction of liver in hemophilia by AAV Factor IX and limitations imposed by the host immune response. Nat Med. 2006;12(3):342–347.

Stieger K, Colle MA, Dubreil L, et al. Subretinal delivery of recombinant AAV serotype 8 vector in dogs results in gene transfer to neurons in the brain. Mol Ther. 2008;16(5):916–923.

SECTION 3 INFORMATION RELATING TO THE CLINICAL TRIAL

3.1 General information about the clinical trial.

EudraCT-number (where available):	2022-500746-16
Deliberate release reference number (where available and applicable):	NA
Title of the clinical trial:	A Phase 2b, Randomized, Double-masked, Multicenter, Dose-ranging, Sham-controlled Clinical Trial to Evaluate Intravitreal JNJ-81201887 (AAVCAGsCD59) Compared to Sham Procedure for the Treatment of Geographic Atrophy (GA) Secondary to Age-related Macular Degeneration (AMD)
Name of principal investigator:	*See section 3.2*
Objective of the study:	The objective of the study is to evaluate the safety, tolerability and efficacy of AAVCAGsCD59 Gene Therapy
Intended start and end date:	August 2023 – February 2025
Number of trial subjects that will take part in the study:	A target of 300 adult 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 2b study are intended for submission to the following countries: Belgium Czech Republic Denmark Germany France Hungary Italy Netherlands Portugal Poland Spain Sweden

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:	UZ Gent
Address Details:	Corneel Heymanslaan 10, 9000 Gent, Belgium
Contact person:	PI Dr. De Zaeytijd
Email Address:	julie.dezaeytijd@ugent.be
Planned activities:	Storage, preparation, in house transport and administration
Containment level:	Level 1 at minimum
Name and contact details of the responsible person[10]**:**	PI Dr. De Zaeytijd julie.dezaeytijd@ugent.be

Organisation Name:	UZ Leuven Gasthuisberg
Address Details:	Herestraat 49, 3000 Leuven
Contact person:	PI Prof. Jacob
Email Address:	julie.jacob@uzleuven.be
Planned activities:	Storage, preparation, in house transport and administration
Containment level:	Level 1 at minimum
Name and contact details of the responsible person[11]**:**	PI Prof. Jacob julie.jacob@uzleuven.be

[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] 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.

Organisation Name:	CHU Liège
Address Details:	Avenue de L'Hòpital 1, 4000 Liège
Contact person:	PI Dr. Locht
Email Address:	blocht@chuliege.be
Planned activities:	Storage, preparation, in house transport and administration
Containment level:	Level 1 at minimum
Name and contact details of the responsible person[12]:	PI Dr. Locht blocht@chuliege.be

Organisation Name:	ZNA Middelheim
Address Details:	Lindendreef 1, 2020 Antwerpen
Contact person:	PI Dr. Ruys
Email Address:	joke.ruys@zna.be
Planned activities:	Storage, preparation, in house transport and administration
Containment level:	Level 1 at minimum
Name and contact details of the responsible person[13]:	PI Dr. Ruys joke.ruys@zna.be

Organisation Name:	Ziekenhuis Oost-Limburg
Address Details:	Synaps Park 1, 3600 Genk
Contact person:	PI Dr. Deghislage
Email Address:	catherine.deghislage@zol.be
Planned activities:	Storage, preparation, in house transport and administration

[12] 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.

[13] 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.

Containment level:	Level 1 at minimum
Name and contact details of the responsible person[14]:	PI Dr. Deghislage catherine.deghislage@zol.be

(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.[15]

Storage will be in line accordance with national legislation. IP shipment should be stored at -80℃ ± 10°C (-70°C to -90°C) in a secure temperature controlled and monitored freezer. During storage, outer packaging must not be separated from inner packaging (e.g., vials should not be removed from outer box). The packaging is designed to protect the drug from breakage and damage and parts should not be separated.

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.

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

Reconstitution (where applicable, summarise reconstitution steps):	A targeted dilution step is not needed for both doses. Vials will be provided with either of the correct vector titre for administration in the clinic.
Pharmaceutical form and strength:	The drug product is supplied as sterile solution of 0.1 mL of a high dose and low dose.
Mode of administration:	Intravitreal injection

[14] 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.

[15] 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.

Information on dosing and administration schedule (in case of repeated dosing):	The AAVCAGsCD59 gene therapy will be administered to a single eye for each participant, chosen as: 1) the eye with the worse visual acuity attributed to GA, or 2) the right eye, if both eyes have equal visual acuity attributed to GA. AAVCAGsCD59 gene therapy will be administered by intravitreal injection using a standardised surgical procedure. Two dose levels (a high or low dose) are administered in this study.
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.

Not applicable.

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, (including contact time) 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 (1- respectively 5-minute contact time Korte et al., 2021), 0.25% 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).

AAVCAGsCD59 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.

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).

Waste containing the genetically modified AAV vector or that has been in contact with the genetically modified AAV vector during preparation and administration will be disposed of as specific hospital or GMO waste.

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.

Samples will be collected from various matrices that may contain the viral vector including lacrimal fluid (tear), saliva, whole blood, serum, and aqueous humor. These samples will be collected at various time points during the study on days 4, 6, 18, and months 1, 3, 6, 12, and 18.

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

d) Explain if there is any non-routine[16] 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,*

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

- *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 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.