PART 1 (COUNCIL DECISION 2002/813/EC)

SUMMARY NOTIFICATION INFORMATION FORMAT FOR THE RELEASE OF GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS IN ACCORDANCE WITH ARTICLE 11 OF DIRECTIVE 2001/18/EC

A. General information

1. Details of notification

(a) Member State of notification BELGIUM
(b) Notification number B/BE/26/BVW2
(c) Date of acknowledgement of notification 23Jan2026
(d) Title of the project
An Open-label, Multicenter, Two Part, Ascending Dose Followed by a Controlled Trial to Assess the Safety and Efficacy of a Subretinal Administration of AAVB-039 in Participants with Stargardt Disease (STGD1) (CELESTE)
(e) Proposed period of release
First Patient First Visit 19May2026
Last Patient First Visit 29Oct2027

2. Notifier

Name of institution or company: AAVantgarde Bio UK Ltd.,

3. GMO characterisation

(a) Indicate whether the GMO is a:

viroid	(.)
RNA virus	(.)
DNA virus	(X)
bacterium	(.)
fungus	(.)
animal	
- mammals	(.)
- insect	(.)
- fish	(.)
- other animal	(.)

specify phylum, class
Phylum: Cossaviricota,
Class: Quintoviricetes

(b) Identity of the GMO (genus and species)
Family: Recombinant AAV039 (Dual AAV8.ABCA4)
Genus: Dependoparvovirus,
Species: Dependoparvovirus

(c) Genetic stability – according to Annex IIIa, II, A(10)

***According to Annex IIIa*:**

The stability in terms of genetic traits is expected to be equivalent to wild-type AAV.

The genetic stability of the AAV8 vector system used for AAVB-039 is supported by the inherent characteristics of AAV and specific design of the dual intein platform.

The core of AAV-039 is a well-established vector platform in genetic therapy with following inherent characteristics of AAV:

- Once delivered into the target cells, the vector DNA typically remains in the nucleus as stable, circular, non-integrating piece of DNA.
- AAV-039 has a very low risk of integrating its genetic payload into host cell's genome, thereby reducing the risk of insertional mutagenesis.
- AAV-039 is expected to remain in the cells as episomes and will not replicate and produce viral particles. The expression cassette will be transcribed and translated by host cell enzymes leading to expression of ABCA4.

AAVB-039 uses proprietary dual AAV intein platform to deliver the gene in two halves:

- The two separate vectors are designed to enter the same target genes, where they combine to produce the full recombinant ABCA4 protein. Several preclinical studies including non-human primates support reliable long-term safety performance of dual AAV8. ABCA4 system.

According to Annex II and Annex A (10):

The batch analysis of drug substance used well-known techniques such as next generation sequencing to ensure and verify that the sequence and size of gene is intact and stable during the manufacturing process.

4. Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?

   Yes (X) No (.)

   If yes, insert the country code(s): NO, IT, NL

5. Has the same GMO been notified for release elsewhere in the Community by the same notifier?

   Yes (X) No ()

   If yes:

   - Member State of notification NO, NL, IT
   - Notification number B/../../…

6. Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?

   Yes (X) No (.)

   If yes:

   - Member State of notification USA
   - Notification number Not Applicable

7. Summary of the potential environmental impact of the release of the GMOs.

The potential impact of releasing AAVB-039 (Dual AAV8.ABCA4) is very low due to its lack of replication ability, limited stability due to natural breakdown in the environment, and low infectivity after being shed from the patient.

Environmental Impacts

Low stability and infectivity

Vector shedding in serum, tears and nasal secretions was dose-dependent and transient in nonclinical studies, indicating that the risk of horizontal transmission is limited to a defined temporal window and overall negligible. Regardless, AAVB-039 (Dual AAV8.ABCA4) vector is likely to be effectively degraded when exposed to activated sludge water in wastewater treatment facilities, thereby posing minimal environmental risk. Even if horizontal gene transfer occurred, AAVB-039 sequences would not confer a selective advantage to bacteria: AAV-039 does not contain any prokaryotic promoters, any antibiotic or other types of resistance genes or any genes, which would enhance or constrain their growth. Therefore, it is unlikely that the vector would interfere with the control of pathogenic microorganisms or that it would have an effect on the natural dynamics of microbial populations or the biogeochemical cycles at any given site in the environment.

Replication incompetence

AAV vectors are non-pathogenic, replication-deficient viral vectors. AAVs do not have a propensity to integrate and, therefore, should present a low risk of gene therapy-related delayed adverse events. Due to the lack of viral Rep and Cap genes, the vector will persist as episome and will not replicate or produce viral particles. Replication incompetence is confirmed as part of release testing and therefore no product would be released that does not meet this specification.

Risk of Transmission

Negligible risk of infection

The risk of caregiver or family member being infected with the shedding of viral particles is negligible due to the amount of viral particles being shed being miniscule and of low infectability. Study personnel will inform the participants and their family of care instructions for the treated eye after administration, including to wear gloves when handling waste and changing dressings, especially when the carer is pregnant, breastfeeding, or immunocompromised.

Risk for vulnerable individuals

Although human infections are common, wild type AAV serotype 8 is not known to be a pathogenic virus in humans and can be classified as a Risk Group 1 biological agent, defined in the EU as ‘one that is unlikely to cause human disease’ according to Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work. Recombinant AAV (rAAV) vectors derived from it are also typically RG1.

Nonetheless, the hospital centres are expected to have adequately trained health care professionals involved in the study in the safe handling of GMOs and to have best biosafety practices implemented in order to minimise any accidental exposure to the product, be it personnel, contact persons or the environment. In view of the low risk AAVB-039 presents to people and the environment and in view of the biorisk management measures applied to even further reduce the exposure to the vector, its overall risk for people and the environment can be evaluated as negligible.

Though the risk is minimal, precautions are still recommended for vulnerable individuals such as pregnant or immunocompromised individuals from potential exposure.

B. Information relating to the recipient or parental organism from which the GMO is derived

1. Recipient or parental organism characterisation:

   (a) Indicate whether the recipient or parental organism is a:

(select one only)

viroid	(.)
RNA virus	(.)
DNA virus	(X)
bacterium	(.)
fungus	(.)
animal	
- mammals	(.)
- insect	(.)
- fish	(.)
- other animal	(.)
(specify phylum, class)	…
other, specify	…

2. Name

(i)	order and/or higher taxon (for animals)	Parvoviridae
(ii)	genus	Dependoparvovirus
(iii)	species	Adeno-associated denpendoparvovirus A…
(iv)	subspecies	
(v)	strain	N/A
(vi)	pathovar (biotype, ecotype, race, etc.)	Serotype 8
(vii)	common name	Adeno-associated virus or AAV

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:

Yes No (.) Not known (X.)

(b) Indigenous to, or otherwise established in, other EC countries:

(i) Yes (.)

If yes, indicate the type of ecosystem in which it is found:

Atlantic	..
Mediterranean	..
Boreal	..
Alpine	..
Continental	..
Macaronesian	..

(ii) No (X.)

(iii) Not known (.)

(c) Is it frequently used in the country where the notification is made?

Yes (.) No (X)

(d) Is it frequently kept in the country where the notification is made?

Yes (.) No (X)

4. Natural habitat of the organism

(a) If the organism is a microorganism

water (.)
soil, free-living (.)
soil in association with plant-root systems (.)
in association with plant leaf/stem systems (.)
other, specify
No natural host known as AAV-039 is non-replicating rAAV8 expressing human ABCA4. AAVB-039 lacks all the viral protein coding sequences. AAVB-039 is derived from AAV which is not currently known to cause disease. The virus causes a very mild immune response, lending further support to its apparent lack of pathogenicity.

(b) If the organism is an animal: natural habitat or usual agroecosystem:
Not Applicable

5. (a) Detection techniques
AAV can be detected by qPCR using primers specific for the viral genome, or by sequencing.

(b) Identification techniques
AAV can be identified by qPCR using primers specific for the viral genome, or by sequencing.

6. Is the recipient organism classified under existing Community rules relating to the protection of human health and/or the environment?
Yes (X) No (.)
If yes, specify
Related to Adeno-associated virus

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (.) No (X) Not known (.)

If yes:

(a) to which of the following organisms:

humans (.)
animals (.)
plants (.)
other (.)

(b) give the relevant information specified under Annex III A, point II. (A)(11)(d) of Directive 2001/18/EC
Not Applicable

8. Information concerning reproduction

(a) Generation time in natural ecosystems:

Not applicable since the vector is not capable of replication

(b) Generation time in the ecosystem where the release will take place:

Not applicable since the vector is not capable of replication

(c) Way of reproduction:

Sexual	N/A
Asexual	N/A

(d) Factors affecting reproduction:

AAV vectors are non-pathogenic, replication-deficient viral vectors. AAVs do not have a propensity to integrate and, in the absence of evidence to the contrary, should present a low risk of gene transfer therapy-related delayed AEs. AAV are considered episomal vectors, although some studies have suggested that low frequency integration events can have oncogenic consequences. Due to the absence of any precedence for oncogenicity from AAV vectors in humans, this risk is considered minimal.

9. Survivability

(a) ability to form structures enhancing survival or dormancy:

(i)	endospores	(.)
(ii)	cysts	(.)
(iii)	sclerotia	(.)
(iv)	asexual spores (fungi)	(.)
(v)	sexual spores (funghi)	(.)
(vi)	eggs	(.)
(vii)	pupae	(.)
(viii)	larvae	(.)
(ix)	other, specify	AAVs have the ability to form extrachromosomal DNA structures called episomes within host cell that remain persistent for extended periods of time.

(b) relevant factors affecting survivability:
Viral particles will not be able to remain intact and infectious for extended periods of time outside the host cell. AAV are effectively degraded in sewage water, most likely due to microbial activity, by hydrolysis, and also by UV radiation at the levels found in nature, and other degrading factors. Replication of AAV cannot occur outside of a host cell, even in the presence of a helper virus due to the deletions of the rep and cap genes. 10% bleach (0.5% sodium hypochlorite) is a routine disinfectant used for disinfecting AAV-contaminated surfaces.

10. (a) Ways of dissemination
Theoretically, it is possible that AAVB-039 could be release to the environment beyond the clinical trial patient receiving treatment with AAVB-039. In this context, the accessible environment is considered to be non-patient humans or unintended human recipients: surgical and medical care staff, relatives and the environment compartment most likely to receive virus shed from the patient. The routine collection and disposal of the virus contaminated clinical waste is not considered to be an environmental release because of the measures routinely taken for biohazardous materials. Waste management and handling procedures are described site specific procedures and in the Sponsor's Pharmacy Manual provided to the site.
However, AAVB-039 is unable to replicate, even in the presence of a helper

virus due to the deletions of the rep and cap genes. The likelihood of replication competent associated adenovirus (rcAAV) is considered low.

(b) Factors affecting dissemination
The routine collection and disposal of the virus contaminated clinical waste is not considered to be an environmental release because of the measures routinely taken for biohazardous materials. Moreover, AAVB-039 unable to replicate, even in the presence of a helper virus due to the deletions of the rep and cap genes. The likelihood of replication competent associated adenovirus (rcAAV) is considered low.

11. Previous genetic modifications of the recipient or parental organism already notified for release in the country where the notification is made (give notification numbers)
Not Applicable

C. Information relating to the genetic modification

1. Type of the genetic modification

(i)	insertion of genetic material	(X)
(ii)	deletion of genetic material	(.)
(iii)	base substitution	(.)
(iv)	cell fusion	(.)
(v)	others, specify …	

2. Intended outcome of the genetic modification
Expression of human ABCA4 protein.

3. (a) Has a vector been used in the process of modification?
Yes (X) No (.)

If no, go straight to question 5.

(b) If yes, is the vector wholly or partially present in the modified organism?
Yes (X) No (.)

If no, go straight to question 5.

4. If the answer to 3(b) is yes, supply the following information

(a) Type of vector

plasmid	(X)
bacteriophage	(.)
virus	(.)
cosmid	(.)
transposable element	(.)
other, specify …	

(b) Identity of the vector
Confidential information cannot be shared due to commercially sensitive information for the Phase 1/2 trial

(c) Host range of the vector

Confidential information cannot be shared due to commercially sensitive information for the Phase 1/2 trial

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype

Yes (X) No (.)

antibiotic resistance (X)
other, specify …

Indication of which antibiotic resistance gene is inserted
Kanamycin

(e) Constituent fragments of the vector
Confidential information cannot be shared due to commercially sensitive information for the Phase 1/2 trial

(f) Method for introducing the vector into the recipient organism

(i)	transformation	(.)
(ii)	electroporation	(.)
(iii)	macroinjection	(.)
(iv)	microinjection	(.)
(v)	infection	(.)
(vi)	other, specify	Confidential information cannot be shared due to commercially sensitive information for the Phase 1/2 trial

5. If the answer to question B.3(a) and (b) is no, what was the method used in the process of modification? Not Applicable

(i)	transformation	(.)
(ii)	microinjection	(.)
(iii)	microencapsulation	(.)
(iv)	macroinjection	(.)
(v)	other, specify	…

6. Composition of the insert

(a) Composition of the insert

The genetic insert of AAVB-039 (also known as Dual AAV8.ABCA4) is the human ABCA4 coding sequence. Given the size of the coding sequence and packaging limitations of AAV, this is split into two active genome sequences, AAV8.5'ABCA4.N-intein (N-ter DS) and AAV8.3'ABCA4.C-intein (C-ter DS).

(b) Source of each constituent part of the insert
Confidential information cannot be shared due to commercially sensitive information for the Phase 1 trial

(c) Intended function of each constituent part of the insert in the GMO

See the intended function of each constituent of N-ter DS genome in **Error! Reference source not found.** and that of C-ter DS genome in **Error! Reference source not found.**.

(e) Location of the insert in the host organism

- on a free plasmid (.)
- integrated in the chromosome (.)
- other, specify

Instead of specific integration, the vector's genetic material persists primarily as extrachromosomal DNA (episomes).

The majority of the AAVB-039 vector DNA forms circular, double-stranded episomes in the nucleus of the host cell. This is the primary mechanism for long-term transgene expression in non-dividing cells, like those in the retina.

With the subretinal administration of AAVB-039 it is anticipated that the vast majority of transgene expression would occur in the retina with some minimal distribution to other ocular tissue as was observed in nonclinical experiments.

(f) Does the insert contain parts whose product or function are not known?
Yes (.) No (X)
If yes, specify …

D. Information on the organism(s) from which the insert is derived

1. Indicate whether it is a:

viroid (.)
RNA virus (.)
DNA virus (.)
bacterium (.)
fungus (.)
animal
- mammals (X)
- insect (.)
- fish (.)
- other animal (.)
(specify phylum, class) …

other, specify …

2. Complete name

(i)	order and/or higher taxon (for animals)	Primates
(ii)	family name for plants	N/A
(iii)	genus	Homo
(iv)	species	Homo Sapiens
(v)	subspecies	N/A
(vi)	strain	N/A
(vii)	cultivar/breeding line	N/A
(viii)	pathovar	N/A
(ix)	common name	Human

3. Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (.) No (X) Not known (.)
If yes, specify the following:

(c) to which of the following organisms:

humans (.)
animals (.)
plants (.)
other ..

(b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism
Yes (.) No (.) Not known (.)

If yes, give the relevant information under Annex III A, point II(A)(11)(d):

N/A

4. Is the donor organism classified under existing Community rules relating to the protection of human health and the environment, such as Directive 90/679/EEC on the protection of workers from risks to exposure to biological agents at work?
Yes (.) No (X)
If yes, specify …

5. Do the donor and recipient organism exchange genetic material naturally?
Yes (.) No (X) Not known (.)

E. Information relating to the genetically modified organism

1. Genetic traits and phenotypic characteristics of the recipient or parental organism which have been changed as a result of the genetic modification

(a) is the GMO different from the recipient as far as survivability is concerned?
Yes (.) No (X) Not known (.)
Specify AAVB-039 viral genome has been significantly modified compared to the original parental wildtype virus (AAV8) in order to render it replication-incompetent. Due to removal of Rep and Cap genes, AAVB-039 is replication-incompetent.
Wildtype AAV (AAV8) requires the presence of a helper virus in order to replicate. However, AAVB-039 is designed based on a helper virus free dual intein platform.

(b) is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?
Yes (X) No (.) Unknown (.)
Specify Due to the removal of the Rep and Cap genes, AAVB-039 is replication incompetent

(d) is the GMO in any way different from the recipient as far as dissemination is concerned?
Yes (X) No (.) Not known (.)
Specify The GMO cannot enter an infectious cycle without the presence of helper function

(e) is the GMO in any way different from the recipient as far as pathogenicity is concerned?
Yes (X) No (.) Not known (.)
Specify Neither wild type AAV (AAV8) nor AAVB-039 are pathogenic to humans or the environment

2. Genetic stability of the genetically modified organism

AAVB-039 is replication incompetent. In the absence of an intrinsic mechanism for genetic variation or instability and based on the known genetic stability of wild type AAV8, the genetic traits of the organism are expected to be stable

3. Is the GMO significantly pathogenic or harmful in any way (including its extracellular products), either living or dead?

Yes (.) No (X) Unknown (.)

(a) to which of the following organisms?

humans (.)
animals (.)
plants (.)
other …

(c) give the relevant information specified under Annex III A, point II(A)(11)(d) and II(C)(2)(i)

N/A

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment

The number of vector genomes can be determined by quantitative PCR with primers specific for vector sequences. This technique, however, is only applicable where sufficient DNA can be recovered for analysis

(b) Techniques used to identify the GMO

The vector is identified by quantitative PCR with primers specific for vector sequences.

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)

Phase 1/2 clinical trial. The purpose of this clinical study will be to assess the safety and efficacy of subretinal administration of AAVB-039 in participants with Stargardt Disease (STGD1).

2. Is the site of the release different from the natural habitat or from the ecosystem in which the recipient or parental organism is regularly used, kept or found?

Yes (X) No (.)

If yes, specify Replication deficient AAV has no natural host.

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference):

The final GMO is not released in the environment but will be administered to patients in a controlled area (clinical site).

(b) Size of the site (m^2): N/A … m^2

(i) actual release site (m^2): … m^2
(ii) wider release site (m^2): … m^2

(d) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:
None

(e) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO
None

4. Method and amount of release

(a) Quantities of GMOs to be released:
Per doses of the Phase 1/2 clinical trial. The Phase 1/2 CELESTE Study is divided into two parts (Part A and Part B). Approximately 75 eligible participants will be enrolled: ~15 in Part A, and 60 in Part B
Treatment will consist of a single subretinal administration of AAVB-039. The study includes a dose escalation phase. Other details of dose are confidential.

(b) Duration of the operation:
Single administration via subretinal surgery anticipated to be completed in up to 4 hours.

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release
Procedures are in place describing methods to store, transport and administer the viral vector. Material at site to be managed as biohazard material and treated as such within current hospital policies and procedures.

5. Short description of average environmental conditions (weather, temperature, etc.)
Confidential information cannot be shared due to commercially sensitive information for the Phase 1/2 trial

6. Relevant data regarding previous releases carried out with the same GMO, if any, specially related to the potential environmental and human health impacts from the release.
AAV vectors are nonpathogenic, replication-deficient viral vectors. AAVs do not have a propensity to integrate and, in the absence of evidence to the contrary, should present a low risk of gene transfer therapy-related delayed AEs. The genetically modified viral vector is not able to survive, disseminate in and/or displace other organisms and it not pathogenic to animals or plants.

G. Interactions of the GMO with the environment and potential impact on the environment, if significantly different from the recipient or parent organism

1. Name of target organism (if applicable) – Not Applicable
(i) order and/or higher taxon (for animals)
(ii) family name for plants (iii) genus

(iv) species
(v) subspecies
(vi) strain
(vii) cultivar/breeding line
(viii) pathovar
(ix) common name

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)

Not Applicable

3. Any other potentially significant interactions with other organisms in the environment
Not Applicable

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur? Not Applicable
Yes (.) No (.) Not known (.)
Give details

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established
Not Applicable

6. Complete name of non-target organisms which (taking into account the nature of the receiving environment) may be unintentionally significantly harmed by the release of the GMO - Not Applicable

(i)	order and/or higher taxon (for animals)	N/A
(ii)	family name for plants	N/A
(iii)	genus	N/A
(iv)	species	N/A
(v)	subspecies	N/A
(vi)	strain	N/A
(vii)	cultivar/breeding line	N/A
(viii)	pathovar	N/A
(ix)	common name	N/A

7. Likelihood of genetic exchange in vivo

(a) from the GMO to other organisms in the release ecosystem:
Not Applicable

(b) from other organisms to the GMO:
Not Applicable

(c) likely consequences of gene transfer:

Not Applicable

8. Give references to relevant results (if available) from studies of the behaviour and characteristics of the GMO and its ecological impact carried out in stimulated natural environments (e.g. microcosms, etc.):
Not Applicable

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)
Not Applicable

H. Information relating to monitoring

1. Methods for monitoring the GMOs

Vector shedding will be closely monitored. Collection of body fluids according to the clinical protocol and risk management plan and quantification using a specific DNA qPCR method.

2. Methods for monitoring ecosystem effects
Vector shedding and release to ecosystem is negligible. The ecosystem effects will also be monitored using specific qPCR method.

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
Transfer of vector genome to study subjects will be detected using specific qPCR method and assessing ABCA4 activity using appropriate clinical read-outs.

4. Size of the monitoring area (m^2)
Not applicable; monitoring techniques will only be used with regards to vector shedding in patients' bodily fluids.

5. Duration of the monitoring
The body fluids of treated subjects will be monitored until found negative (three consecutive negative samples) for the presence of vector DNA.

6. Frequency of the monitoring
Vector shedding will be assessed prior AAVB-039 infusion and at all visits after receiving AAVB-039 until negative or below limit of quantification on at least three consecutive occasions.

I. Information on post-release and waste treatment

1. Post-release treatment of the site
The process of decontamination should be discussed with the local environmental health and safety officer and/or biosafety committee before receipt of any AAVB-039 product on site so that an appropriate plan and supplies are in place. Briefly, decontamination of the IMP administration room by standard procedures will be used after administration. Any material or surface in contact with the product will be decontaminated with hypochlorite solution, 10% bleach (0.5% sodium hypochlorite), or other detergent-based disinfectant. Any other disposable instruments or other materials used during the dose preparation procedure will be disposed of in a manner consistent with the standard practice of the institution for potentially biohazardous materials.

2. Post-release treatment of the GMOs
Since the product will be supplied by the manufacturer to the hospital pharmacy in a subject-to-subject manner, no unused product will remain at the hospital centre after administration to patients. Any open vials or unused material will be destroyed by decontamination according to local hospital procedures and in compliance with national biohazard regulations and standards.
All unused vials need to be kept in the required storage conditions (-60°C);
Used/partly used vials will be discarded at the site following requirements for biohazardous waste. Consumables used in the preparation and administration of the GMO that may have come in contact with AAVB-039 will be decontaminated prior to disposal as biohazardous waste. Liquid waste will be decontaminated using an appropriate chemical disinfectant. Disinfectants that are effective against AAV include 10% bleach (0.5% sodium hypochlorite), or other detergent-based disinfectant.

3. (a) Type and amount of waste generated

The type and amount of waste generated:

- Empty/partly empty vials containing AAVB-039 residue (guide tube, cannula, injection needles and syringes). The number of vials of AAVB-039 required per patient is dependent on the dose cohort and the body weight of the patient.
- Materials used for the preparation and administration of the study product, e.g. saline bag, IV administration set, syringes, needles etc.
- Personal protective equipment, e.g. gloves
- Components used for collecting body fluids samples after administration

3. (b) Treatment of waste

Sharps such as needles will be disposed of in adequate sharp containers and incinerated. Disposables such as syringes, tubing and catheters will be decontaminated by immersion in a chemical disinfectant with virucidal activity before incineration. All the surgical materials (surgery tools, linens) and surgery waste (gloves, compresses) will be collected and autoclaved before washing and sterilisation or incineration. All non-disposable surgical equipment will be cleaned using a chemical disinfectant with proven virucidal activity (e.g. hypoclorite solution) and then sterilized by autoclaving according to standard practices of the institution.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread

The solution of AAVB-039 for sub-retinal injection will be prepared by the hospital pharmacist or designee in a contained area inside a flow cabinet in the hospital centres. The appropriate personal protection equipment (PPE) (laboratory coat, safety glasses and gloves etc.), clean air and single use instruments in theatres should be used when preparing IMP and handling study samples to minimise the risk of contamination. In case of spillage the affected area, lineated with absorbing material, will be decontaminated using appropriate disinfectants with virucidal activity. A spill kit will be available at all times during the administration procedure.

The IP manual will be provided to staff at the site, for the management and disposal of AAVB-039 virus, which should be followed by all personnel responsible for transporting, preparing, administering, disposing of the medicinal product or equipment/consumables that have come into contact with the product designated for use in clinical study, that must be disposed of as biohazardous waste.

AAVB-039 drug product is stored in vials. Staff will be advised that care must be taken when manipulating vials and that the use of needles should be kept to a minimum. In the event of injury, staff will follow local institutional procedures as well as those listed in Table 1.

Table 1 Management of incidents related to AAVB-039

Incident	Procedure
Accidental spillage	All spills must be wiped with absorbent gauze pad and the spill area must be disinfected using a bleach solution, 10% bleach (0.5% sodium hypochlorite), followed by alcohol wipes. The use of 6000 ppm (mg/L) bleach solution can generate ocular irritation or oropharyngeal, oesophageal, and gastric burns and should be reserved for minor surface spill treatment. All clean up materials must be double bagged and disposed of per local hospital procedures and in compliance with national biohazard regulations and standards for handling of biohazardous waste.
Sharps injury	The use of needles is to be kept to a minimum. In the event of injury, report to Principle Investigator (PI). PI to notify CRA.
Contact with skin and clothing	The appropriate personal protection equipment (PPE) (laboratory coat, safety glasses and gloves etc.) should be used to minimise the risk of contamination and contact with skin and clothing. Remove contaminated clothing. Flush area with large amounts of water. Use soap. Seek medical attention
Contact with eyes	Flush with water while holding eyelids open for at least 15 minutes. Seek medical attention immediately.

2. Methods for removal of the GMO(s) of the areas potentially affected
All spills of AAVB-039 must be wiped with absorbent gauze pad and the spill area must be disinfected using a bleach solution, 10% bleach (0.5% sodium hypochlorite) followed by alcohol wipes. The use of 6000 ppm (mg/L) bleach solution can generate ocular irritation or oropharyngeal, oesophageal, and gastric burns and should be reserved for minor surface spill treatment. All clean up materials must be double bagged and disposed of per local hospital procedures and in compliance with national biohazard regulations and standards for handling of biohazardous waste.

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread
Administration of AAVB-039 will occur only within a controlled hospital setting; therefore, it is not anticipated that it will come into contact with plants, animals or soil. Furthermore, AAVB-039 is not capable of infecting plants or microbes.

4. Plans for protecting human health and the environment in the event of an undesirable effect
Although no undesirable effects are expected, safety recommendations and guidance on the management of incidents related to AAVB-039 are provided in the safety instructions for investigators and staff. All patients will be carefully monitored for any adverse reactions during this study. An independent data monitoring committee (iDMC) will be responsible for monitoring safety data from the study.

K. References

Wu, Z., H. Yang and P. Colosi (2010). "Effect of genome size on AAV vector packaging." Mol Ther **18**(1): 80-86.

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