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

In order to tick one or several possibilities, please use crosses (meaning x or X) into the space provided as (.)

A. General information

1. Details of notification

(a)	Member State of notification	Republic of Ireland
(b)	Notification number	B/IE/21/01
(c)	Date of acknowledgement of notification	01/12/2021
(d)	Title of the projects	

EXPLORE: A Phase II, Outcomes, Assessor-Masked Multicentre, Randomised Study to Evaluate the Safety and Efficacy of Two Doses of GT005 Administered as a Single Subretinal Injection in Subjects with Geographic Atrophy Secondary to Age-Related to Macular Degeneration.

HORIZON: A Phase II, Open-Label, Outcomes-Assessor Masked, Multicentre, Randomised, Controlled Study to Evaluate the Safety and Efficacy of Two Doses of GT005 Administered as a Single Subretinal Injection in Subjects with Geographic Atrophy Secondary to Dry Age-Related Macular Degeneration.

Proposed period of release: June 2022 until July 2026

2. Notifier

Name of institution or company: Gyroscope Therapeutics Limited

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 …

(b) Identity of the GMO (genus and species)
Parvoviridae
Genus: Dependovirus
Species: AAV-derived replication-deficient viral vector

(c) Genetic stability – according to Annex IIIa, II, A(10)
In general DNA viruses have greater genetic stability than RNA viruses. GT005 is unable to replicate, even in the presence of a helper virus, since the genes essential for replication are deleted. The genetic modifications made to generate GT005 do not change the non-pathogenic nature of AAV2 and, equally, the modifications are not anticipated to have any effect on the host range, stability or survival of the GMO outside of the host when compared to that of the wild-type virus. The stability in terms of genetic traits is therefore expected to be equivalent to wild-type AAV. DNA of wild type AAV and of AAV-based vectors persists in transduced cells as circular (extrachromosomal) episomal concatemers in human tissues (Chen et al. 2005, Schnepp et al. 2005, Schnepp et al. 2009). However, due to the lack of viral *rep* and *cap* genes, GT005 is expected to remain in the cells as episomes and will not replicate and produce viral particles.

4. Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?
Yes (.) No (X)
If yes, insert the country code(s)

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: DE
- Notification number: B/DE/20/PEI3944 (EXPLORE)
  B/../../… (HORIZON) Not available on Eur. Com. GMO register

- Member State of notification: ES
- Notification number: B/ES/19/24 (EXPLORE)
  B/ES/20/13 (HORIZON)

- Member State of notification: FR
- Notification number: (contained use, not applicable)

- Member State of notification: NL
- Notification number: B/NL/19/024 (EXPLORE)

- Member State of notification: PL
- Notification number: (contained use, not applicable)

Please use the following country codes:

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

- Member State of notification: Australia
- Notification number: Not applicable

- Member State of notification: UK
- Notification number: Not applicable (contained use)

Phase I study with GT005 NCT03846193 and Phase II studies EXPLORE (NCT04437368) and HORIZON (NCT04566445

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

The potential for unintended spread within the environment is considered low. Transmission of GT005 to an unintended human recipient is likely to be isolated since the product will be administered to and handled by a limited number of individuals in a hospital environment. Any inadvertent exposure will be self-limiting; GT005 has been engineered to be replication defective, even in the presence of a helper virus, as it lacks the *rep* and *cap* genes required for rescue/packaging. The likelihood of GT005 to become persistent or invasive is therefore negligible.

The selective advantage conferred on GT005 is that it has been rendered replication-defective through omission of the Rep and Cap sequences. Furthermore, the transgene is not expected to confer any advantage to GT005 in terms of survival in the environment. None of the genetic modifications made to wild type AAV2 during construction of GT005 would be expected to enable the transfer or maintenance of genetic material into the environment (outside its obligate host species) or have an effect on sensitivity to inactivating agents or survivability in the environment. The potential for environmental interactions with non-target organisms is therefore considered negligible.

The likelihood of gene transfer to species other than humans and (some) primates is low, given the host preference of AAV. The natural host of wild type AAV2 is humans. AAV does not infect plants or other microbes and is not known to be involved in environmental processes. As far as (unintentional) gene transfer to humans and primates is concerned, the likelihood is low given that GT005 is modified from wild type AAV2 and is unable to replicate independently, even in the presence of a helper virus, as it lacks the *rep* and *cap* genes required for rescue/packaging. These genetic modifications do not affect its natural host range and tissue tropism.

No immediate and/or delayed environmental impact is expected. The potential for environmental impact of the interactions between GT005 and humans is negligible. Wild type AAV2 is not known to be involved in environmental processes. It does not respire and

does not contribute to primary production or decomposition processes. It does not display any metabolic activity in its virion form.

GT005 will be administered by subretinal injection to eligible patients by medical professionals in a hospital environment. GT005 cannot replicate in the human body; shedding through tears and saliva and biodistribution through blood is expected to be low and transient, based on a non-clinical assessment, interim clinical data for GT005 from the FOCUS study and clinical experience with other subretinally administered rAAV2 products. Based on interim vector shedding data from patients treated in Cohorts 3 and 4 (medium or high dose) in the GT005 Phase I/II FOCUS clinical study, clinical vector is expected to be cleared (no further shedding) from patients within week 1 of treatment.

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)	N/A
(ii)	genus	Dependoparvovirus
(iii)	species	Parvoviridae
(iv)	subspecies	Adeno-associated virus
(v)	strain	N/A
(vi)	pathovar (biotype, ecotype, race, etc.)	Serotype 2
(vii)	common name	Adeno-associated virus type 2 AAV-2

3. Geographical distribution of the organism

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

Yes (X) No (.) Not known (.)

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

(i) Yes (X)

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

Atlantic	(X)
Mediteranean	(X)
Boreal	(X)
Alpine	(X)
Continental	(X)
Macaronesian	(X)

(ii) No (.)

(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	Specific hosts are humans and non-human primates.

(b) If the organism is an animal: natural habitat or usual agroecosystem:

Not applicable.

5. (a) Detection techniques

Quantitative Polymerase Chain Reaction (qPCR)
Viral culture
Enzyme linked Immunosorbent Assay (ELISA)
Western blotting
Next Generation Sequencing (NGS)

(b) Identification techniques

As in B5a.

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: Wild type AAV is not classified in Risk Groups 2, 3 or 4 according to Directive 2000/54/EC on the protection of workers from risks related to exposure to

biological agents at work (Annex III of the Directive). It is designated a Risk Group 1 biological agent, defined as 'one that is unlikely to cause human disease' in the EU.

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

AAVs are frequently found in humans and animals, but they are not pathogenic, virulent, allergenic, or a carrier (vector) of a pathogen. The known host range includes humans and non-human primates. In natural conditions, wild type AAV is found to transmit to humans in the presence of a helper virus. It does not activate latent virus and is not able to colonise other organisms

8. Information concerning reproduction

(a) Generation time in natural ecosystems:

Not applicable since the vector is not capable of replication even in the presence of a helper virus since it lacks the *rep* and c*ap* genes required for rescue/packaging.

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

Not applicable since the vector is not capable of replication as mentioned above.

(c) Way of reproduction: Sexual N/A Asexual N/A

(c) Factors affecting reproduction:

Reproduction of wild-type AAV is dependent on co-infection with helper virus (e.g. adenovirus or herpesvirus). Replication ability depends on *rep* and c*ap* viral sequences. GT005 is an attenuated (recombinant) AAV: genes essential for DNA replication and DNA packaging into an AAV particle have been removed.

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 In the latent form, AAVs have the ability to form extrachromosomal concatemers that remain episomal for extended periods of time.

(b) relevant factors affecting survivability:
Wild type AAV is a non-enveloped virus, with a stable capsid. There have been extensive studies on AAV vectors showing that exposure to heat, UV radiation, or extreme pH can inactivate recombinant vector particles. For example, AAV particles are resistant pH 3 to 9 and can resist heating at 56 ^{o}C for 1 hour (Berns and Bohenzky, 1987).

None of the genetic modifications made to wild type AAV2 during construction of GT005 would be expected to have an effect on the mode of transmission, survivability in the environment, or sensitivity to inactivating agents.

10. (a) Ways of dissemination
Wild-type AAV dissemination is mainly through the airway, although sexual transmission has been hypothesised.

(b) Factors affecting dissemination
Co-infection with a helper virus. However, GT005 is not capable of replication regardless of the presence of a helper virus.

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)
…, B/../../… Not previously notified.

C. **Information relating to the genetic modification**

1. Type of the genetic modification

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

2. Intended outcome of the genetic modification
Deletion of the *rep* and *cap* viral sequences, leading to the loss of replication ability and the insertion of the transgene for the treatment of subjects with geographic atrophy due to age-related macular degeneration.

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

Three DNA plasmids are used for the production of GT005.

(c) Host range of the vector

The plasmids used in the manufacture of GT005 are capable of replication in bacteria. The host range, tissue specificity, and tropism of AAV is determined by the capsid. The capsid of GT005 is composed of the same proteins as wild type AAV2, therefore, the host range and tropism of GT005 vector and wild type AAV2 are the same.

(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

Plasmid 1 encodes the CFI transgene expression cassette flanked by AAV2 inverted terminal repeat sequences

Plasmid 2 encodes the AAV2 *rep* and *cap* genes

Plasmid 3 encodes the viral helper functions for vector production

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

(i)	transformation	(.)
(ii)	electroporation	(.)
(iii)	macroinjection	(.)
(iv)	microinjection	(.)
(v)	infection	(.)
(vi)	other, specify	Transfection

5. If the answer to question B.3(a) and (b) is no, what was the method used in the process of modification?

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

6. Composition of the insert

(a) Composition of the insert
Complement factor cDNA with promoter and enhancer elements.

(b) Source of each constituent part of the insert
The transgene cDNA is human in origin. The other sequences in the genome and promoter and enhancer elements are synthetic, viral and mammalian in origin.

(c) Intended function of each constituent part of the insert in the GMO
The human transgene cDNA encodes a recombinant form of a native human complement factor. The other elements of the vector ensure packaging of the genome and expression of the gene.

(d) Location of the insert in the host organism

- on a free plasmid (.)
- integrated in the chromosome (.)
- other, specify Mainly extrachromosomal as episomal concatemers in the host cells.

(e) 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 (.)
- insect (.)
- fish (.)
- other animal (.)
(specify phylum, class) …

other, specify Human – complement factor I cDNA.

2. Complete name

(i)	order and/or higher taxon (for animals)	Primates
(ii)	family name for plants	N/A
(iii)	genus	*Homo*
(iv)	species	*H. sapiens*
(v)	subspecies	N/A
(vi)	strain	*Sapiens*
(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 (X) Not known (.)

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

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 (X) No (.) Not known (.)

AAV can integrate into the host DNA. In the absence of Rep proteins, ITR-flanked transgenes encoded within recombinant AAV can form circular concatemers that persist as episomes in the nucleus of transduced cells.

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

(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 GT005 lacks the *rep* and *cap* genes so is replication incompetent even in the presence of a helper virus.

(d) is the GMO in any way different from the recipient as far as dissemination is concerned?
Yes (X) No (.) Not known (.)
Specify GT005 cannot enter an infectious cycle even in the presence of helper function.

(e) is the GMO in any way different from the recipient as far as pathogenicity is concerned?
Yes (.) No (X) Not known (.)
Specify GT005 is not known to be pathogenic.

2. Genetic stability of the genetically modified organism

The genetic traits of the modified organism are expected be stable considering the known genetic stability of the parent wild type AAV and also because the therapeutic activity of GT005 is not dependent on replication of the rAAV vector.

Homologous recombination between GT005 and wild type AAV could occur if both were present in the same cell that was also infected with a helper virus. Such recombination could only result in the exchange of the transgene expression cassette with the Rep and Cap genes of the wild type virus. However, it is not possible for the AAV genome to contain both *rep/cap* genes and the transgene, as this is beyond the packaging limit of the virion. Moreover, the regions of homology between GT005 and a potential co-infecting wild type AAV would be limited to the ITRs, since the *rep* and *cap* genes have been removed from GT005; this is therefore likely to further decrease the possibility of recombination.

The only mechanism by which the transgene would be mobilised is through a triple infection of the same cell by GT005 (containing the transgene), wild type AAV (providing the Rep and Cap functions) and a helper virus. It this occurred, it would result in the production of further wild type AAV and further GT005 vector particles, which could still lack the *rep* and *cap* genes and would thus not be self-sustaining.

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 …

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

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment
Quantitative polymerase chain reaction (qPCR).

(b) Techniques used to identify the GMO
Quantitative polymerase chain reaction (qPCR).

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)
The purpose of the release is for clinical studies is to evaluate the safety and efficacy of GT005 for the treatment of subjects with geographic atrophy due to age-related macular degeneration.

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 GT005 will be administered by subretinal injection to eligible patients by medical professionals in a few hospital centres. It should be noted that humans are natural hosts for AAV, infections are asymptomatic and AAV is not known to cause any noticeable pathology. Similarly, dose-dependent administration of AAV/based GMOs to humans has been shown to be safe.

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference):
Planned participating sites:
Surgical site and follow-up site: UPMC Whitfield Hospital Institute of Eye Surgery, 2 Buttlerstown, Waterford, X91 DH9W.

(b) Size of the site (m^2): … m^2
(i) actual release site (m^2): … m^2
(ii) wider release site (m^2): … m^2
Not applicable

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:
Not applicable.

(d) 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:
It is anticipated that 4E13 vector genome particles will be released as part of the EXPLORE study, and 8E13 for the HORIZON study. A total of 12E14 vector genomes particles will therefore be released under this notification.

(b) Duration of the operation:
Up to 1 hour.

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release
The investigational medicinal product will be supplied to selected hospital centres ensuring no long-term storage. Since GT005 is considered a type 1 risk GMO and is used in a clinical trial, its usage will be restricted to hospital facilities which will have undergone a site feasibility assessment for their capability to manage biologic hazardous and infectious material, including storage and waste management. Tier 1 biosafety measures will be implemented. All involved personnel at the site will be trained in best biosafety practices to be applied during thawing, transport to the administration room, precautions during administration and disposal of any biological waste. Such training involves, among others, wearing protective clothing and gloves, the presence of a spill kit and the decontamination of waste prior to disposal as biohazardous waste.

5. Short description of average environmental conditions (weather, temperature, etc.)
Hospital treatment room and ambient indoor conditions for administration to clinical trial subjects. The investigational medicinal product (GT005) will be stored at ≤ -60°C, thawed at room temperature and kept at room temperature until patient administration (on the same working day that IMP preparation occurs).

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.
None

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)

(i)	order and/or higher taxon (for animals)	Primates
(ii)	family name for plants	N/A
(iii)	genus	*Homo*
(iv)	species	*H. sapiens*
(v)	subspecies	sapiens

(vi)	strain	N/A
(vii)	cultivar/breeding line	N/A
(viii)	pathovar	N/A
(ix)	common name	Human

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)
The gene sequence encoding the transgene will be delivered into the target retinal cells of patients where it is expected to persist episomally.

3. Any other potentially significant interactions with other organisms in the environment
None.

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?
Yes (.) No (X) 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
There is no known ecosystem in which GT005 could be successfully established.

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

None

(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	…

7. Likelihood of genetic exchange in vivo

(a) from the GMO to other organisms in the release ecosystem:
Highly unlikely. GT005 will be injected into the subretinal space and is unable to replicate. Due to the low numbers of vector DNA copies potentially released into the environment through shedding, horizontal gene transfer is highly unlikely.

(b) from other organisms to the GMO:
Highly unlikely. Exposure to replication competent AAV (rcAAV) may theoretically be mediated by the investigational product by either generation of rcAAV by recombination of production plasmids during manufacture, or homologous

recombination of an existing wild type AAV with GT005 in a patient's cells (co-infected with a helper virus). In terms of rcAAV, the potential routes of exposure will be the same as for GT005, however the likelihood of transmission of rcAAV is considered even lower than that of GT005, given that GT005 is tested for absence of rcAAV as part of quality control (QC) testing. The likelihood of a homologous recombination event *in vivo* is also very low, requiring a triple infection of the same cell, followed by a recombination event. Furthermore, the regions of homology between GT005 and wild type AAV are limited to the ITRs since the *rep* and *cap* genes are deleted from the recombinant vector.

(c) likely consequences of gene transfer:
The genetic material from the *rep* and *cap* genes together with the transgene would be too large in size to be packed in an AAV capsid. Thus, it is highly unlikely that the recombination would result in a replication-competent vector containing the transgene. Any recombination would result in the expression of the transgene by infected cells.

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.):
None

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)
None known or predicted since wild type AAV is not known to be involved in any bio-geochemical process.

H. Information relating to monitoring

1. Methods for monitoring the GMOs
Patients are being followed up for expression of CFI in the study for authorisation.

2. Methods for monitoring ecosystem effects
No monitoring is considered necessary

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
The vector genome contains unique sequences, which are not expected to be found in clinical samples not exposed to the vector. PCR based methods using vector genome specific primers are being used for detecting the presence of vector DNA sequences in blood, urine, tears, and saliva for patients treated with GT005.

4. Size of the monitoring area (m^2)
… m^2
Not applicable.

5. Duration of the monitoring
Observation of subjects will be by means of post-administration surveillance. Subjects will be followed for 96 weeks post-dosing. After the final follow-up visit, all subjects will be enrolled into a dedicated clinical trial for long-term follow-up.

6. Frequency of the monitoring
During the protocol defined study visits, as approved by the regulatory authorities.

I. Information on post-release and waste treatment

1. Post-release treatment of the site
Decontamination of the IMP administration room will be employed after administration according to Pharmacy manual and local procedures.

2. Post-release treatment of the GMOs
Any open vials will be destroyed according to Pharmacy manual and local procedures and unused material will inactivated / destroyed on site or by a waste company off-site according to local biosafety guidelines.

3. (a) Type and amount of waste generated

- Used vials of the Investigational Medicinal Product
- Used preparation equipment; syringes, needles vials
- Used injection kit
- Containers used to transport potentially contaminated equipment to and from storage facility
- Personal Protective Equipment used during dose preparation and administration
- Equipment used for collecting patient samples after administration

It is anticipated that no more than 50 mL of product waste will be generated in the EXPLORE study, and no more than 120 mL of product waste for the HORIZON study. This makes the total waste produced under this notification will be no more than 170 mL.

3. (b) Treatment of waste
Any disposable consumables/instruments used during the handling, dose preparation and administration procedures, including syringes and needles used for the dilution of the IMP, will be disposed of according to local procedures in a manner consistent with the standard practice of the institution for Risk Group 1 GMOs. In the medical facility, this will involve containment in sharps bins or clearly marked bags (e.g. biohazard, medical waste) prior to autoclaving and/or incineration either on or off site as per local institutional guidelines. All open vials containing GT005 will be retained/returned to pharmacy and stored until the unmasked CRA has performed reconciliation. Any opened and/or unopened GT005, and/or expired Treatment Kits, diluent vials (used and unused) and administration vials used during the preparation and administration of GT005 will be destroyed on site (once directed by the unmasked CRA), according to local procedures in a manner consistent with the standard practice of the institution for Risk Group 1 GMOs. In the medical facility, this will involve temporary containment in sharps bins or clearly marked bags (e.g. biohazard, medical waste) prior to autoclaving and/or incineration either on or off site. Records of the receipt and dispensing of the IMP will be kept by the site (pharmacy/storage unit) to provide complete accountability of all used and unused IMP.

J. Information on emergency response plans

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

GT005 will be administered in a controlled, hospital environment. Accidental exposure and/or spillage of GT005 will be mitigated by the standard precautions in the Pharmacy Manual which will be provided to all clinical staff involved in the preparation and administration of the product. In case of a spill, the affected area will contained, and the area decontaminated using a viricidal disinfectant as per local guidelines and institutional procedures and according to the manufacturer's instructions. A spill kit provided by the sponsor will be available at all times during the administration procedure. Details are given in the investigational medicinal product (IMP) Pharmacy Manual, describing the handling of the IMP in the pharmacy and the administration procedures that will be handed over to the site during the site initiation visit (prior to starting the study).

2. Methods for removal of the GMO(s) of the areas potentially affected

Method of removal depends on the type of exposure:

Skin contact:	Wash the affected area with soap and water. If the skin is not broken, wash with viricidal soap and plenty of water. Obtain medical attention.
Eye contact:	Immediately flush eyes with copious amounts of water or eyewash solution while holding the eyelid(s) open. Obtain medical attention
Needle stick:	Encourage bleeding of the wound. The area is immediately washed well with soap and water. Obtain medical attention
Inhalation of aerosol:	If inhaled, move person into fresh air. Obtain medical attention
Ingestion:	Rinse mouth with water. Obtain medical attention.

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread

Not applicable since exposure of plants or animals is not expected. The predicted habitat of GT005 is humans where it is expected to persist in a lysogenic state. GT005 is a disabled version of wild type AAV2, modified by deletion of the *rep* and *cap* genes rendering it unable to replicate even in the presence of a helper virus.

4. Plans for protecting human health and the environment in the event of an undesirable effect

No undesirable effects are expected. AAVs are frequently found in humans and animals, but they are not pathogenic, virulent, allergenic, or a carrier (vector) of a pathogen. The known host range includes humans and non-human primates. In natural conditions, wild type AAV is found to transmit to humans in the presence of a helper virus. It does not activate latent virus and is not able to colonise other organisms.