Environmental Protection Agency
An Ghníomhaireacht um Chaomhnú Comhshaoil

Headquarters
PO Box 3000
Johnstown Castle Estate
County Wexford
Ireland

Consent to a deliberate release of a GMO into the environment for purposes other than for placing on the market

GMO Register Number:	G0784-01
SNIF Reference Number:	B/IE/21/01
GMO Notifier:	Gyroscope Therapeutics Limited Rolling Stock Yard 188 York Way London N7 9AS United Kingdom
Location of the Part B Deliberate Release:	UPMC Whitfield Hospital Institute of Eye Surgery 2 Butlerstown Waterford X91 DH9W

Consent to the deliberate release of a GMO into the environment for purposes other than for placing on the market under Article 18(5)(a) of the Genetically Modified Organisms (Deliberate Release) Regulations, 2003 (S.I. No. 500 of 2003).

GMO Register No. G0784-01

SNIF No. B/IE/21/01

The Agency in exercise of the powers conferred on it by the Genetically Modified Organisms (Deliberate Release) Regulations, 2003 (S.I. No. 500 of 2003) hereby grants consent to:

Gyroscope Therapeutics Limited
Rolling Stock Yard
188 York Way
London N7 9AS
United Kingdom

To carry out the following activity for purposes other than for placing on the market:

The administration of gene therapy treatment GT005 comprising a recombinant adeno-associated virus serotype 2 (AAV2) carrying an expression cassette containing DNA encoding human Complement Factor I to patients with geographic atrophy secondary to age-related macular degeneration.

The aforementioned activity and patient follow-up will be performed in the following locations:

UPMC Whitfield Hospital Institute of Eye Surgery
2 Butlerstown
Waterford
X91 DH9W

The period of release extends from the date of grant of these consent conditions to July 2026.

SEALED by the Seal of the Agency on this the 5th day of July 2022

PRESENT when the seal of the Agency was affixed hereto:

Ray Cullinane
Authorised Person

DECISION

The Agency, in exercise of the powers conferred on it by the Genetically Modified Organisms (Deliberate Release) Regulations, 2003 (S.I. No. 500 of 2003) for the reasons hereinafter set out, grants this consent to:

Gyroscope Therapeutics Limited
Rolling Stock Yard
188 York Way
London N7 9AS
United Kingdom

To carry out the deliberate release into the environment for purposes other than for placing on the market in the following location:

UPMC Whitfield Hospital Institute of Eye Surgery
2 Butlerstown
Waterford
X91 DH9W

Subject to nine conditions and the annexes attached hereto.

REASONS FOR THE DECISION

The Agency is satisfied on the basis of the information provided that, subject to compliance with the conditions of this consent, the notifier will ensure that all appropriate measures are taken to avoid adverse effects on human health and the environment. Furthermore, the Agency believes that the risks to human health or the environment from the deliberate release of these GMOs are negligible.

In arriving at its decision, the Agency considered the following aspects:

i. the patient receiving the treatment insofar as they are part of the general population and the wider environment;

ii. the potential risk of the GMOs moving from the patient to the general population and the consequences of such a risk; and

iii. potential environmental concerns.

The Agency did not consider the risks that the treatments might pose for the patient as an individual volunteering to participate in the trial.

In reaching this decision, the Agency has considered the notification and supporting documentation received in respect of the notification and the report of its inspector.

The consent is granted in accordance with Article 18(5)(a) of the Genetically Modified Organisms (Deliberate Release) Regulations, 2003 (S.I. No. 500 of 2003).

INTERPRETATION

Agency	The Environmental Protection Agency (EPA).
Competent Authority	The Environmental Protection Agency is the Competent Authority for the purposes of the GMO (Deliberate Release) Regulations, 2003 (S.I. No. 500 of 2003).
Consent	Consent issued in accordance with Article 18(5) of the GMO (Deliberate Release) Regulations, 2003, (S.I. No. 500 of 2003).
Deliberate Release	Means any intentional introduction into the environment of a genetically modified organism or a combination of genetically modified organisms for which no specific containment measures are used to limit their contact with, and to provide a high level of safety for, the general population and the environment. This deliberate release relates to the performance of a clinical trial using a GMO in patients with geographic atrophy secondary to age-related macular degeneration.
Directive	Means 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.
Environmental Risk Assessment	Means an evaluation, carried out in accordance with the Second Schedule of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003, of risks to human health or the environment, whether direct or indirect, immediate or delayed, which the deliberate release or the placing on the market of a genetically modified organism may pose.
Facility	Facility in this instance relates to the facility in UPMC Whitfield Hospital Institute of Eye Surgery, Waterford where the deliberate release clinical trial will be carried out and patients will be followed up.
GMO	Genetically Modified Organism means an organism, other than a human being, in which the genetic material has been altered in a way that does not occur naturally by mating or natural recombination or by a combination of both.

	For the purposes of this trial, the GMO is GT005 comprising a recombinant adeno-associated virus serotype 2 (AAV2) carrying an expression cassette containing DNA encoding human Complement Factor I (CFI).
GMO Register	A register of GMO users in Ireland, which is available for viewing on the Agency's webpage and at Agency Headquarters. Information provided in the register includes details of the notifier, the location and date or dates of the deliberate release, a description and intended uses of the GMO involved and the purpose of the deliberate release activity.
GMO Regulations	Genetically Modified Organisms (Deliberate Release) Regulations, 2003 (S.I. 500 of 2003).
Micro-organism	Micro-organism means any microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material, including viruses, viroids, and animal and plant cells in culture.
Notification	A notification means the submission of required information to the competent authority.
Notifier	Means any legal or natural person submitting a notification or, where the context so requires, any legal or natural person responsible for a deliberate release or for a placing on the market, or for meeting any other requirement of the Genetically Modified Organisms (Deliberate Release) Regulations, 2003 in relation to a deliberate release or a placing on the market. The Notifier is: Gyroscope Therapeutics Limited Rolling Stock Yard 188 York Way London N7 9AS United Kingdom
Obligation	A person who carries out a deliberate release or placing on the market shall ensure that all appropriate measures are taken to avoid adverse effects on human health or the environment arising from the deliberate release or placing on the market.

Organism	Means any multicellular, unicellular, subcellular, or acellular entity capable of replication or of transferring genetic material whether by natural or artificial processes or such other matter as may be prescribed by the Minister (Minister of the Environment, Climate & Communications).
Principal Investigator	A Principal Investigator (PI) is the individual responsible for the conduct of the clinical trial at the clinical trial site.
SOPs	Standard Operating Procedures.

Consent Conditions for GMO Register Entry No: G0784-01

Condition 1 Scope

1.1 This consent is for the purposes of compliance with the Genetically Modified Organisms (Deliberate Release) Regulations, 2003 (S.I. No. 500 of 2003) only, in relation to the carrying out of deliberate release trials (clinical trials) as specified in Condition 2.

1.2 Nothing in this consent shall be construed as negating the statutory obligations or requirements of the notifier, UPMC Whitfield Hospital Institute of Eye Surgery, Waterford or the Principal Investigator under any other enactments or regulations.

1.3 No modifications to the deliberate release, as described in the notification and supporting information submitted to the Agency, shall take place without the prior written approval of the Agency.

Reason: To clarify the scope of the consent

Condition 2 Location of the Clinical Trial

2.1 This consent is for the purposes of conducting a clinical trial at the following location from the date of grant of these consent conditions to 31st July 2026:

UPMC Whitfield Hospital Institute of Eye Surgery
2 Butlerstown
Waterford
X91 DH9W

Reason: To clarify the location of the clinical trial

Condition 3 Duration of the Clinical Trial

3.1 This consent is for the purposes of conducting a clinical trial from the date of grant of these consent conditions to 31st July 2026. No deliberate release of the GMO shall take place after this date.

Reason: To clarify the duration of the clinical trial

Condition 4 Management of the clinical trial

4.1 The clinical trial shall be carried out at UPMC Whitfield Hospital Institute of Eye Surgery, Waterford by pharmacological, consultant and nursing staff suitably trained in the handling and manipulation of the GMO.

4.2 The responsibility assigned in Condition 4.1 shall include responsibility for reception, storage, transportation, preparation, and administration of the GMO. It shall also include responsibility for samples taken from patients treated with the GMO as described in the notification as well as the disposal

and treatment of all GMO contaminated materials used during the clinical trial.

4.3 Access to the pharmacy, theatre prep-room, theatre, and recovery and/or patient's room where the GMO will be stored, prepared, administered to the patient, and where the patient will be moved to post-administration for overnight observation, respectively, will be restricted to trained delegated staff.

4.4 The notifier shall provide the name and contact details of persons in the employ of:

- Gyroscope Therapeutics Limited; and
- UPMC Whitfield Hospital Institute of Eye Surgery, Waterford;

who each have responsibility for overseeing the performance of this clinical trial at UPMC Whitfield Hospital Institute of Eye Surgery, Waterford. These details shall be submitted to the Agency two weeks prior to the commencement of the clinical trial. Any change to this designation during the trial shall be notified immediately to the Agency.

4.5 All communications with the Agency in relation to this trial shall be through the person identified to the Agency under Condition 4.4.

4.6 The notifier shall, prior to commencement of the clinical trial submit to the Agency a copy of the agreement put in place with UPMC Whitfield Hospital Institute of Eye Surgery, Waterford describing the delegation of responsibility as required by Conditions 4.1 and 4.2.

4.7 The notifier is responsible for ensuring personnel involved in performing specifically assigned tasks and/or having access to the facility during the trial shall be appropriately trained and:

4.7.1 Made aware of the risks relating to the GMO associated with the trial;
4.7.2 Made aware of the possible routes of exposure to the GMO and the procedures to follow in the event of accidental exposure.

4.8 Prior to the commencement of the deliberate release clinical trial the necessary facilities for the storage, transport, manipulation, and inactivation of the GMO shall be made available at the trial location as stipulated under Condition 2.1.

Reason:	**To make provision for management of the activity on a planned basis having regard to the desirability of ongoing assessment, recording, and reporting of matters affecting the environment**

Condition 5 Duty of the notifier to inform the Agency of new information

5.1 If, following the granting of this consent, new information relevant to the deliberate release becomes available, or there is an unintended change to the

deliberate release which could have consequences for the risks to human health or the environment, the notifier shall:

5.1.1 Immediately take the necessary measures to protect human health and the environment;
5.1.2 Inform the Agency as soon as the new information becomes available or the unintended change is known;
5.1.3 Inform the Agency as soon as possible of such further measures the notifier has taken or proposes to take in relation to the matters concerned.

5.2 The Agency may, following an evaluation of the matters identified in Condition 5.1:

5.2.1 Modify the consent conditions; or,
5.2.2 Suspend or terminate the deliberate release.

5.3 In the event that the Agency suspends the deliberate release further to the evaluation of the new information or unintended change, the deliberate release activity shall not resume until such time as the notifier obtains written consent from the Agency permitting its recommencement.

Reason:	**To provide and update information on the clinical trial**

Condition 6 Containment measures to be used at the Deliberate Release Site

6.1 In order to keep the exposure of humans and the environment to the GMOs to the lowest practicable level and to ensure a high level of safety, the notifier shall apply:

6.1.1 The general principles of Good Microbiological Practice and of Good Occupational Safety and Hygiene (reproduced in *Annex II* attached);

6.1.2 Containment measures 3, 9, 13, 14, 15, 17 and 18, corresponding to the Class of the GMM (containment level 1 measures) as set out in Table IA of the Fourth Schedule of the GMO (Contained Use) Regulations (2001 to 2010), (reproduced in *Annex III* attached).

6.2 The notifier, the Principal Investigator (condition 4.4) and all personnel involved in the performance of this clinical trial shall apply the clinical trial protocol and all safety instructions as described in the notification and supporting documentation submitted to the Agency.

6.3 Standard Operating Procedures (SOPs).

6.3.1 Prior to the commencement of the clinical trial, the notifier shall ensure that the following SOPs relating to the performance of the GMO clinical trial within the facility, are implemented:

- Measures for limiting access to the facility;
- Work apparel, personal protective equipment;

- Receipt of the GMO;
- Secure storage of the GMO;
- Transport, movement and handling of the GMO;
- Preparation of the GMO for patient administration;
- Administration of the GMO to the patient;
- Treatment of GMO spillages;
- Cleaning and disinfection of non-disposable equipment;
- Storage and treatment of GMO contaminated waste;
- Maintenance of records relating to the receipt and storage of the GMO, staff training and the removal of GMO waste for inactivation;
- Worker protection measures to be taken during the release;
- Protocol for needlestick injury.

6.3.2 Eye protection shall be worn at all times during the receipt, transport, preparation, administration and disposal of the GMO.

6.3.3 SOPs shall be made available to all relevant clinical trial personnel at least two weeks prior to trial commencement and to the Agency upon request.

6.3.4 SOPs shall be reviewed annually.

Reason:	**To ensure proper management of the clinical trial and to avoid adverse effects on human health and the environment arising from the clinical trial**

Condition 7 Worker Protection Measures to be taken during the clinical trial

7.1 The notifier shall draw up and maintain a list of all persons with access to the facility while the GMO is in use. This list shall be made available to the Agency on request.

7.2 Pregnant staff members will not be present in the theatre.

7.3 The notifier shall implement worker protection measures during the clinical trial. These measures shall apply to all staff involved in the execution of the clinical trial or with access to the facility during that time. An SOP setting out these worker protection measures, and their implementation shall be made available to all relevant clinical trial staff and the Agency at least two weeks prior to trial commencement.

Reason:	**To comply with the legislation and to avoid adverse effects on human health and the environment**

Condition 8 Waste Management

8.1 Disposable GMM contaminated waste shall be disposed of into appropriately labelled, closed, unbreakable, leak-proof containers while awaiting collection by an authorised waste contractor. Waste storage containers shall

be appropriately labelled as containing GM waste and shall display biohazard signs.

8.2 Spill kits shall be made available at all times during preparation and administration of the GMO.

8.3 Waste shall be stored securely prior to collection to prevent the risk of human or environmental exposure to the waste. Access to the waste storage facility shall be restricted to authorised persons.

8.4 GMM contaminated sharps waste shall be disposed of into sharps bins and sealed when three quarters full.

8.5 All GMM contaminated waste shall be inactivated by validated means before disposal.

8.6 GMM contaminated waste shall be collected and shall be transported from the clinical trial site to the site of waste inactivation by a contractor authorised in accordance with the provisions of the appropriate National and European legislation and protocols.

8.7 GMM contaminated waste sent off-site for inactivation shall be transferred only to an appropriate facility which is licenced by the Agency for the inactivation of Class 1 GMM waste under the (GMO (Contained Use) Regulations 2001 to 2010.

8.8 GMM waste inactivation records shall be retained within the facility for inspection by the EPA on request.

Reason:	**To ensure proper management and destruction of GMO waste so as to avoid adverse effects on human health and the environment**

Condition 9 Record Keeping and Reporting to the Agency

9.1 Record keeping and reporting to the Agency shall be in accordance with Annex I attached.

9.2 The notifier shall inform the Agency of trial commencement within two weeks of the first patient receiving treatment.

9.3 The notifier shall submit a report to the Agency, in the format set out under Commission Decision 2003/701/EC[1], (adapted for the release of a human medicinal product) on or before the 31 July 2026. This report shall include the following information:

- The results of the deliberate release;

[1] Commission Decision of 29 September 2003 establishing pursuant to Directive 2001/18/EC of the European Parliament and of the Council a format for presenting the results of the deliberate release into the environment of genetically modified higher plants for purposes other than placing on the market *(notified under document under C(2003) 3405)* (2003/701/EC)

- A post-release evaluation of the risks to human health and the environment; and,
- Where appropriate, a statement on the results of the clinical trial in relation to any product, or type of product, in respect of which consent to placing on the market may be sought.

9.4 All records/reports (including GMO inactivation records) shall be retained by the notifier at UPMC Whitfield Hospital Institute of Eye Surgery for a period of 12 months following trial completion. Prior to trial commencement, the notifier shall inform the EPA of the position of the person in UPMC Whitford Hospital with responsibility for these records/reports.

9.5 The notifier shall inform the Agency of trial completion within two weeks of the last patient receiving treatment.

9.6 Training records signed by all staff in receipt of training relating to the GMO deliberate release activity, shall be approved and maintained by the notifier. These records shall be made available to the Agency on request.

Reason:	**To maintain written records of the clinical trial and make provision for the reporting to the Agency of any impacts of the completed clinical trial and associated risks**

Annex I

SCHEDULE OF REPORTING / MAKING INFORMATION AVAILABLE

Deadline	**Information to be submitted to the EPA**	**Information to be made available to clinical trial staff**
To be provided **2 weeks** prior to trial commencement.	The notifier shall provide the name and contact details of persons in the employ of: • Gyroscope Therapeutics Limited; and • UPMC Whitfield Hospital Institute of Eye Surgery Waterford; who each have responsibility for overseeing the performance of this clinical trial at UPMC Whitfield Hospital Institute of Eye Surgery, Waterford. (Condition 4.4). Any change to this designation shall be notified to the Agency immediately, (Condition 4.4) Notifier shall make available to the Agency • SOP on worker protection measures (Condition 7.3)	Notifier shall make available to clinical trial staff: • SOPs set out under Condition 6.3.1 (Condition 6.3.3) • SOP on worker protection measures (Condition 7.3)
To be provided prior to trial commencement.	Notifier Date of trial commencement (Condition 9.2)	
	Notifier A copy of the agreement put in place with UPMC Whitfield Hospital Institute of Eye Surgery, Waterford describing the delegation of responsibility, (Condition 4.6)	Notifier shall make available to clinical trial staff: • Risks relating to the GMO • Possible routes of exposure to the GMO • Procedures to follow in the event

		of accidental exposure (Condition 4.7)
	Notifier Shall implement SOPs set out under Condition 6.3.1 (Condition 6.3.1)	
	Notifier The position of the person responsible for reports/ records (Condition 9.4)	
To be made available to the Agency on request.	SOPs set out under condition 6.3.1 (Condition 6.3.3)	
	List of all with access to the facility while the GMO is in use (Condition 7.1)	
	GMM waste inactivation records (Condition 8.8)	
	Training records (Condition 9.6)	
To be provided to the Agency within two weeks of the last patient receiving treatment .	Notifier Notification of trial completion (Condition 9.5)	
To be provided to the Agency on trial completion.	Report in the format set out under Commission Decision 2003/701/EC (Condition 9.3)	

Annex III

Table IA showing containment measures required.

Refer to condition 6.1

Table IA

Containment measures for contained use of genetically modified micro-organisms in a laboratory

Measures		**Containment levels**			
		1	2	3	4
1	Laboratory Suite: Isolation	Not required	Not required	Required	Required
2	Laboratory: sealable for fumigation	Not required	Not required	Required	Required
Equipment					
3	Surfaces resistant to water, acids, alkalis, solvents, disinfectants, decontamination agents and easy to clean	**Required for bench**	Required for bench	Required for bench and floor	Required for bench, floor, ceiling and walls
4	Entry to laboratory via airlock	Not required	Not required	Optional	Required
5	Negative pressure relative to the pressure of the immediate environment	Not required	Not required	Required	Required
6	Extract and input air from the laboratory should be HEPA-filtered	Not required	Not required	Required	Required for input and extract air
7	Microbiological safety cabinet	Not required	Optional	Required	Required
8	Autoclave	On site	In the building	En suite	Double-ended autoclave in laboratory

System of work					
9	Restricted access	**REQUIRED**	Required	Required	Required
10	Biohazard sign on the door	Not required	Required	Required	Required
11	Specific measures to control aerosol dissemination	Not required	Required to minimise	Required to prevent	Required to prevent
12	Shower	Not required	Not required	Optional	Required
13	Protective Clothing	**Suitable protective clothing**	Suitable protective clothing; footwear optional	Suitable protective clothing and footwear	Complete change of clothing and footwear before entry and exit
14	Gloves	**REQUIRED**	Optional	Required	Required
15	Efficient vector control (e.g. for rodents and insects)	**REQUIRED**	Required	Required	Required
Measures		**Containment levels**			
		1	2	3	4
Waste					
16	Inactivation of genetically modified micro-organisms in effluent from hand-washing sinks or drains and showers and similar effluents	Not required	Not required	Optional	Required
17	Inactivation of genetically modified micro-organisms in contaminated material and waste	**REQUIRED**	Required	Required	Required
Other Measures					
18	Laboratory to contain its own equipment	**REQUIRED**	Not required	Optional	Optional
19	Observation window or alternative to enable occupants to be seen	Optional	Optional	Optional	Required

For the purpose of this table:

(1) In measure 1, "isolation" means that the laboratory is separated from other areas in the same building or is in a separate building.

(2) In measure 4, "airlock" means that the entry must be made through a chamber isolated from the laboratory. The clean side of the airlock must be separated from the restricted side by changing or showering facilities, or by interlocking doors.

(3) In measure 5, "negative pressure relative to the pressure of the immediate environment" is only required for a class 3 contained use where airborne transmission can occur.

(4) "HEPA" means high efficiency particulate air.

(5) In measure 6, where viruses which are not capable of being retained by HEPA filters are used in class 4 contained use, extra requirements shall be provided for extract air.

(6) In measure 8, "en suite" means that where the autoclave is located outside the laboratory in which the contained use is being carried out but within the laboratory suite, validated procedures shall be in place to ensure the safe transfer of material into the autoclave and to provide a level of protection equivalent to that which would be achieved if the autoclave were in the laboratory.

Sealed by the seal of the Agency on this the 5th day of July 2022.

PRESENT when the seal of the Agency was affixed hereto:

Ray Cullinane
Authorised Person