This Report has been cleared for submission to the Board of Directors by Marie O'Connor

Signed: Marie O'Connor Date: 08/06/2022

Office of Environmental Sustainability

INSPECTOR'S REPORT

TO:	Board of Directors
FROM:	Bernie Murray, Inspector - Environmental Licensing Programme
DATE:	8th June 2022
RE:	Notification from Gyroscope Therapeutics Limited, Rolling Stock Yard, 188 York Way, London N7 9AS, United Kingdom, under Part II of the GMO (Deliberate Release) Regulations (S.I. 500 of 2003) to conduct a clinical trial using a GMO (GMO Register No: G0784-01).

Applicant:	Gyroscope Therapeutics Limited Rolling Stock Yard 188 York Way London N7 9AS United Kingdom
GMO Register Entry No:	G0784-01
SNIF No[1]:	B/IE/21/01
Notification under Article 14(1) of S.I. No 500 of 2003:	The deliberate release of a genetically modified organism for purposes other than placing on the market (Part B Release – Clinical Trial).
Timeframe for EPA's Decision under Article 18(5) of S.I. No 500 of 2003:	A person shall not deliberately release a genetically modified organism (GMO) for purposes other than placing on the market unless consent in writing has been granted by the EPA. The EPA shall communicate its decision (either grant consent with or without conditions or refuse consent) in writing to the notifier within 90 days of receipt of the notification.
Date of receipt of notification under Article 14 of S.I. No 500 of 2003:	01/12/2021

[1] Summary Notification Information Format (SNIF). Summary of the notification forwarded to the European Commission for circulation to all member states.

Request for additional information under Article 19 of S.I. 500 of 2003:	21/01/22 & 14/02/22	13/04/22 & 22/04/22	04/05/22
Additional Information submitted under Article 19 of S.I. 500 of 2003:	21/03/22	29/04/2022	31/05/2022
Date by which decision is required:	8th June 2022		
Representations to the EPA relating to this notification under Article 16 of S.I. 500 of 2003:	0		

Introduction

Gyroscope Therapeutics Limited, Rolling Stock Yard, 188 York Way, London N7 9AS United Kingdom, sought the consent of the Environmental Protection Agency (EPA) on 1 December 2021 to perform a Phase 2 clinical trial investigating GT005. Gyroscope Therapeutics Limited is in this instance both the sponsor[2] and the notifier.

The Genetically Modified Organism (GMO) is a gene therapy treatment called GT005. It will be administered to patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

AMD (which results in a blurred area or blank spot in the centre of vision) is the most common cause of blindness among the elderly in the industrialised world. AMD typically affects people aged 50 and over. Approximately 67 million people in the EU are currently affected with AMD and due to population ageing this number is expected to increase in the coming years.

There are two types of AMD: wet and dry. Dry AMD is the predominant form making up to 90% of cases. GA is considered the late/advanced stage form of dry AMD. Loss of visual function because of GA is considered irreversible and usually affects both eyes. Currently, there are approved therapies for wet AMD but not for GA.

This trial involves two separate Phase II clinical studies (termed "EXPLORE" and "HORIZON") each evaluating the safety and efficacy of two doses of GT005. The trials will be run concurrently and will be approximately the same length. The trials use the same GMM, the purpose of the deliberate release is the same and it will be carried out over a defined period of time. This complies with of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003 which permits the application to be made under a single notification.

GT005 uses a modified version of Adeno-associated virus (AAV) to deliver a functional gene to the eye that will help the eye to make more of a naturally occurring human protein called Complement Factor I (CFI). The purpose of the trials is to test whether a single administration of GT005 is effective at slowing the progression of the disease and that it is safe to use in patients with GA secondary to AMD.

[2] A sponsor oversees or pays for a clinical trial and collects and analyses the data

Considerations for the Board

Role of the EPA in reviewing this notification

The Agency's responsibility under the Genetically Modified Organisms (Deliberate Release) Regulations (Article 18, S.I. 500 of 2003) is to evaluate the risks posed by the proposed deliberate release for human health or the environment and to give consent to the release only if satisfied that it will not result in adverse effects to human health or the environment.

The responsibility of the Agency relates to the wider environment and the general population. In its review of the application, ELP has considered:

- the patient receiving the treatment insofar as they are part of the general population and/or the wider environment;
- the potential risk of the GMO moving from the patient to the general population and the consequences of such a risk; and,
- potential risks for the environment at large.

Description of the Genetically Modified Micro-Organism for use in the proposed clinical trial

The Genetically Modified Organism (GMO), GT005, is a recombinant, non-replicating adeno-associated serotype 2 viral vector (rAAV2). The expression cassette contains DNA encoding for human Complement Factor I (CFI), the therapeutic transgene. The GMO is constructed using recombinant DNA technology from wild-type AAV2 (wtAAV2) which is non-pathogenic, single-stranded DNA genome that requires a helper virus such as adenovirus or herpes simplex virus for replication.

Purpose of the proposed deliberate release

The purpose of the proposed clinical trial is to test whether a single administration of GT005 is effective at slowing the progression of the disease and that it is safe to use in patients with GA secondary to AMD.

Three doses of GT005 will be administered across the two studies as follows:

- EXPLORE: a low dose or a high dose;
- HORIZON: a medium dose or a high dose.

Each patient recruited to either EXPLORE or HORIZON will receive a single dose of GT005. The high dose is the same for both studies.

Proposed location of the deliberate releases

The storage, preparation and administration of the GMO and follow-up assessments of treated patients will take place at UPMC Whitfield Hospital Institute of Eye Surgery, 2 Butlerstown, Waterford.

The notifier originally proposed two sites, UPMC Whitfield Hospital, where GMO administration and patient follow up would take place and UPMC Kildare Hospital where patient follow-up would take place. UPMC Kildare Hospital was subsequently removed from the notification with surgical and GMO administration and follow-up activities now taking place at the UPMC Whitfield Hospital site only. An amended notification and SNIF were submitted.

In accordance with Article 17 of the GMO (Deliberate Release) Regulations, S.I. No 500 of 2003, where there have been amendments to the notification (in the form of new information or a modification to the proposed release) which could have consequences for the risks to human health or the environment, the notifier is required to submit a new notification and the Agency is required to treat it as if it were a new notification. In this instance the removal of a site was not viewed as having consequences for the risks to human health or the environment as the release is now confined to one site.

Timeframe for the proposed clinical trial

It is proposed that treatment of clinical trial patients will take place at the aforementioned hospital from the date of grant of the consent to July 2026.

Enrolment into the EXPLORE and HORIZON studies is expected to be completed by October 2023 and follow-up of enrolled patients will continue for 96 weeks post dosing i.e., through to September 2025. The notifier has factored in an additional 9 months (October 2025 to July 2026) as a contingency to account for any unexpected delays that may occur.

Once patients have completed their 96-week post-dosing follow-up, they will be invited to participate in a long-term follow-up study for a further three years.
According to the notifier around 30 patients will be treated during the EXPLORE and HORIZON studies.

The Notifier

The notifier and trial sponsor, Gyroscope Therapeutics Limited, is situated in the UK.

GM clinical trials involving the use of GT005 were notified by Gyroscope Therapeutics Limited in Germany, Spain, and the Netherlands in 2020 under the deliberate release Directive[3]. Consents were issued by the German and Dutch Competent Authorities. No information is given with regard to Spain. France, Poland and the UK previously conducted GM clinical trials with GT005 under the contained use Directive[4].

A Principal Investigator (PI) will be responsible for the conduct of the clinical trial.

In accordance with Article 18(5) of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003, the Agency is required to respond to the notifier in writing indicating that consent is either granted with or without conditions or refused, with reasons for the refusal.

The notifier is situated in the U.K. and is not the Principal Investigator. Given that any consent that may be granted will be issued to the notifier, neither the PI (in the employ of the Institute of Eye Surgery) nor the clinic at which the trial will be carried out (UPMC Whitfield Hospital), will bear any responsibility to the EPA to ensure compliance with the consent. Legal advice sought by ELP in this regard in 2018 indicated that while there are practical difficulties in terms of enforcement, it is not a bar to granting consent.

Advice from the Commission in 2021 indicated that regardless of whether the notifier is established in the EU, the notifier remains subject to the requirements of the Directive as transposed into the law of the Member State in which it carries out the deliberate

[3] Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms.

[4] Directive 2009/41/EC on the contained use of genetically modified micro-organisms

release and is liable to any penalties provided under the national law of that member state in case of breach of their obligations.

Once consent has been granted, Article 22 of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003 allows the Agency to modify the conditions of, suspend or terminate the deliberate release, where it becomes aware of information, which in its view, could have significant consequences for the risks to human health or the environment (Condition 5.2).

Condition 4.4 requires the notifier to provide the name and contact details of a person employed by Gyroscope Therapeutics Limited responsible for overseeing the trial at the UPMC Whitfield Hospital site. All communications between the Agency and Gyroscope Therapeutics Limited will be through this person (Condition 4.6).

Risk Assessment according to the information supplied in the notification.

The GMO

The GMO (GT005) is constructed from wild type AAV serotype 2 (wtAAV2) using recombinant DNA technology. The AAV2 *rep* and *cap* genes have been removed and replaced with an expression cassette containing DNA encoding human Complement Factor I (CFI), the therapeutic transgene, and regulatory elements.

The recipient organism, AAV2, is not pathogenic, virulent, or allergenic. Humans are a natural host, and it is designated a Risk Group 1 biological agent, according to Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work. A Risk Group 1 biological agent is defined as 'one that is unlikely to cause human disease'. These characteristics of the wild type virus are not different in the GM version of the virus. The genetic modifications do not change the non-pathogenic nature of AAV2.

WtAAV2 requires a helper virus (such as adenovirus or herpes simplex virus) for replication to occur in cells. GT005 is unable to replicate independently, even in the presence of a helper virus since it lacks the essential *rep* and *cap* genes.

The Insert

The transgene is Complement Factor I (CFI). Mutations in the CFI gene have been associated with a predisposition to develop diseases associated with complement system dysregulation, including Age-related Macular Degeneration (AMD).

GT005 uses recombinant AAV (rAAV) to deliver a functional gene to the eye that will help the eye to make more of the naturally occurring human protein CFI.

Hazards associated with the release of replication competent AAVs

GT005 vector is replication deficient even in the presence of a helper virus but replication competent AAV (rcAAV) could theoretically be formed during production of the GMO, although risk of rcAAV formation is predicted to be negligible. Each batch of GT005 is tested for the absence of rcAAV as part of the QC testing prior to release of the product for use.

Hazards associated with insertional mutagenesis

In the absence of the *rep* gene, rAAV is incapable of site-specific integration into the genome, (as is the case with wtAAV). Rather, it exists outside the chromosome as

episomes. The possibility of integration into the chromosome is extremely rare, however, there is a theoretical risk that random insertion may occur. Based on current knowledge, GT005 does not present any additional risks with respect to genomic integration when compared to wtAAV.

Hazards associated with vertical /germline transmission

WtAAV dissemination is mainly through the airways. Shedding data has revealed limited systemic vector distribution outside of the ocular space and the risk of vector DNA/rAAV being present in the testes and ovaries is considered to be low. Nonetheless, as a measure of caution, persons participating in the trial are required to use two forms of contraception, one of which is a barrier method, for 90 days post dosing.

Possibility of recombination

Homologous recombination between GT005 (providing the transgene) and wtAAV (providing the *rep* and *cap* genes) could occur if both were present in the same cell, co-infected with a helper virus (required to facilitate replication). Such a recombination event would result in the exchange of the transgene with the *rep* and *cap* genes of the wild type virus. 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. Therefore, it is highly unlikely that the recombination would result in a replication competent vector containing the transgene.

Three-way infection of a cell as described above is expected to be a rare event and would only result in the production of more wtAAV and more GT005 vector particles (which would still lack *rep* and *cap* genes and consequently could not be self-sustaining).

Shedding

GT005 will be administered by subretinal injection to eligible patients by medical professionals in a hospital environment. GT005 cannot replicate in the human body following administration and therefore the absolute amount of GMO that could theoretically be shed would not exceed the dose administered.

There is minimal dissemination of the vector outside of the ocular space. This has been demonstrated in GT005 non-clinical studies which have shown that subretinal administration of GT005 results in the dosing site (retina, retinal pigment epithelium and choroid – integral parts of the eye) yielding the highest average vector concentrations compared to the other tissues analysed. This is consistent with published literature on other AAV2-gene therapies administered into the eye.

Based on interim vector data from patients in the GT005 Phase I/II FOCUS clinical study (available in October 2021) the clinical vector is expected to be cleared (no further shedding) locally and systemically from patients within 1 week of treatment. Again, these data are in line with the shedding profile observed with other subretinally administered AAV-based products.

CFI protein is ubiquitously expressed in the general population and therefore potential unintended recipients would have had lifelong exposure to CFI.

Immune response

Administration of the GMO will elicit an immune response to AAV capsid very similar to natural infection with wtAAV. Interim clinical immunogenicity data on GT005 as of December 2020 show that antibodies to CFI have not been detected in any subject and at any time point.

Risks to the Environment

WtAAV does not infect plants or other microbes and is not known to be involved in environmental processes.

Due to the low numbers of vector DNA copies potentially released into the environment through shedding, horizontal gene transfer is deemed unlikely.

Storage, preparation and administration of the vector

The GMO will be shipped frozen on dry ice to UPMC Whitfield Hospital in Waterford. The hospital pharmacy will receive the GMO which will be stored at ≥-60°C, separate from other medications, in a restricted access facility until released for patient administration. The freezer temperature will be monitored.

The GMO kit, containing a GT005 vial, a diluent vial and an empty administration vial will be delivered as close to the day of planned administration as possible. On the day of administration, the kit will be removed from the freezer and thawed at ambient temperature prior to transportation to the theatre. Once thawed, GT005 and the diluent will be in liquid form and will be maintained at 15-25°C until patient administration. Dilution of GT005 is required to prepare the low and medium doses. It is not required for the high dose. A backup dose per patient will also be delivered. Once it is confirmed that the backup dose is not required arrangements will be for it to be returned to the supplier. Therefore, the GMO will not be held in the Pharmacy for any longer than is necessary.

GMO preparation/dilution will take place in a sterile prep area in the theatre prep-room, adjacent to the theatre department and will be administered to the patient by a trained vitreoretinal surgeon (PI) in the theatre department. Following administration, the patient will be moved to a single room and kept overnight for observation.

Single use instruments will be used for the preparation and administration of the GMO.

Pharmacy staff preparing and transporting the GMO from the pharmacy to the theatre, and the PI and theatre staff will wear suitable protective clothing (Condition 6.1.2) comprising gloves, scrubs and/or surgical gown or equivalent (as identified in the notification), and eye protection (Condition 6.3.2).

Worker protection measures taken during the release

The GMO will be prepared/diluted using aseptic technique in the theatre prep room by the pharmacist and a pharmacy technician, with a spill kit available in the event of a spillage (Condition 8.2).

The GMO will be packed in a hazardous chemical transport box, to facilitate transportation from the pharmacy to the theatre (a journey of <5minutes). The transport box will also contain a spill kit in case of accidental release.

Personnel handling the GMO through its receipt, transport, preparation, administration or disposal will be required to adhere to appropriate safety procedures and to wear

Personal Protective Equipment such as laboratory coat or scrubs or surgical gown or equivalent as appropriate, gloves and eye protection (Condition 6.3).

Pregnant staff members will not be present in theatre (Condition 7.2).

The notifier, Gyroscope Therapeutics Limited, will provide training (Condition 4.7) and will also be present on-site during treatment of at least the first 6 patients.

The trial is expected to involve approximately 30 patients. GMO administration via sub-retinal injection will entail the use of single use instruments that will subsequently be disposed of in sharps bins.

It is possible for personnel to come into contact with GT005 during preparation or administration. This could occur via accidental spillage of the product solution on surfaces, accidental needle-stick injury, skin contact (through mucous membranes) with the product or aerosolised product. A needlestick injury protocol is in place (Condition 6.3). With regard to exposure to the GMO, the viral vector is replication incompetent therefore the only effect could be a marginal increase in CGI if any and an immune response to AAV2 capsid.

Waste production, treatment and disposal

Clinical waste bins (black lidded, rigid, yellow waste bins) containing absorbent will be situated in the pharmacy, theatre, and the recovery room and/or the patient's room ahead of patient admission. Each bin will be marked GMO and will be used for the purposes of GMO waste collection.

Contaminated waste arising from the

- storage of GT005 in the pharmacy;
- preparation and administration of GT005 in the theatre;
- care of the patient following administration of the GMO (tissues/dressing containing tears potentially contaminated with GT005)

will be placed directly into the clinical waste bin at each specific location (pharmacy, theatre and recovery or patients' room respectively) and sealed as soon as possible thereafter.

Sharps waste (e.g., syringes, needles, pipettes, sharps containing bodily fluids) are deposited directly into sharps bins and sealed. The sealed clinical waste bins will be removed by authorised operatives to an external, controlled access, clinical waste compound. All waste bins within the compound will be locked. The waste will be collected and transported to SRCL (Ltd) (G0163-01, W0055-02) from where it will be shipped abroad for incineration. A cert of destruction will be issued to UPMC Whitfield after treatment. GMM waste inactivation records are required to be retained at UPMC Whitfield Hospital Institute of Eye Surgery for a period of 12 months following trial completion (Conditions 8.8 and 9.4).

Condition 8 dealing with waste management, requires that all GMM contaminated waste be inactivated by validated means before disposal.

Gyroscope Therapeutics Limited will supply spill kits which will be available at all times during the preparation and administration stages (Condition 8.2) to counteract any spillage. Surface decontamination will be carried out using the virucidal disinfectant "Virusolve" which is active against AAV.

Duration and frequency of monitoring

Patients will be followed up for expression of CFI in the study. Blood and vitreous samples will be taken at UPMC Whitfield Hospital for all patients treated with GT005. Samples will be sent to a central laboratory in the Netherlands for testing. Patients will be followed for 96 weeks post-dosing. After the final follow-up visit, all patients will be invited to participate in a long-term follow-up study for a further three years.

Representations made in respect of the notification

Any person may make a representation in respect of matters relating to the deliberate release of the GMO within a 28-day period beginning on the date of publication of the notice in the newspaper, in accordance with Article 16 of the GMO (Deliberate Release) Regulations, S.I. No 500 of 2003. The notice was published in "Irish Times" newspaper on 10th December 2021, and the period for submission of representations ended on 18th January 2022 (taking account of the Christmas period). The Agency received no representations during this period.

Review of the notification by the EPA and external consultation

The Agency's review of the notification involved both an external and internal review.

External Review

Review of the GMO Advisory Committee

The GMO Advisory Committee

The Agency consulted the GMO Advisory Committee (GMO AC) on this application and received three replies.

One GMO AC member expressed no concerns for the safety of human health or the environment as a result of this trial. A second GMO AC member concluded that GT005 represents good use of GMO technology and it does not pose a threat to the natural environment

A third GMO AC member raised a number of questions, largely in relation to biosafety aspects of the trial, which were clarified with the notifier. The notifier submitted a revised notification.

Consultation with other regulatory bodies and government departments

A separate application was submitted to the Health Products Regulatory Authority (HPRA) by the notifier under Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use on 28th September 2021. The performance of this trial has been authorised by the HPRA and a condition included that the trial cannot commence in Ireland until such time as EPA approval is in place.

Other EU member states

The Agency submitted the SNIF to the European Commission in accordance with Article 18(1) of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003. The Commission published the SNIF to all other EU member states for comment (17/12/2021). The Agency did not receive any comments or observations from other member states. The most recently updated version of the SNIF was published on the Commission's webpage on 10/05/2022.

Internal review

The EPA has reviewed the notification and the additional information received.

A site inspection of the UPMC Whitfield Hospital site, was carried out on 21 April 2022 during which I met with the Biosafety team comprising the Head of Quality and Safety and the Clinical Trials Manager at the Institute of Eye Surgery, the Director of Pharmacy and the Director of Quality and Patient Safety, UPMC Ireland, the General Manager and the Quality Manager, UPMC Whitfield.

The life cycle of the GMO from its receipt at the facility, storage prior to use, delivery to theatre, reconstitution and patient administration, cleaning and waste handling procedures post administration and disposal of GM contaminated material were addressed during the site inspection.

In terms of risk to human health or the environment the measures in place are proportionate and adequate in the context of the intended trial.

Condition 6.2 requires the notifier/consent holder, the Principal Investigator, and all personnel to perform the deliberate release in accordance with the information provided in the notification and documentation submitted in support of the notification.

Conclusions

The notification provided under Article 14 of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003 and the additional information provided by the notifier in response to a request for further information under article 19(1), contains all the mandatory information.

The GMO (GT005) is a recombinant, replication-deficient, AAV-based vector that will be administered to patients with geographic atrophy secondary to age-related macular degeneration. AAV is not pathogenic to humans and is not known to be involved in environmental processes. Recombinant AAV lacks the viral *rep* and *cap* genes and consequently it will not replicate or produce viral particles. The risk of recombination is negligible. The containment level required to control the overall risk is containment level 1.

Fee payable to the EPA

The appropriate fee of €3,000 as outlined in the Part IV of the GMO (Deliberate Release) Regulations (S.I. 500 of 2003) was paid in respect of a notification for a proposed deliberate release for purposes other than placing on the market.

Recommendation

Based on the notification and additional information provided by the notifier under the GMO (Deliberate Release) Regulations it is considered unlikely that GT005 will have adverse effects on human health or on the environment in the context of the intended clinical trial, provided that the trial protocol, all the proposed conditions of the trial and foreseen safety measures will be applied.

On this basis I recommend that consent be granted, subject to conditions, to Gyroscope Therapeutics Limited, Rolling Stock Yard, 188 York Way, London N7 9AS, United Kingdom, for the deliberate release of GT005, during a clinical trial under Part B of the GMO (Deliberate Release) Regulations, S.I. No 500 of 2003 at UPMC Whitfield Hospital, Waterford. The clinical trial will assess the safety and efficacy of the administration of a single dose of the GMO (GT005) to patients with geographic atrophy secondary to age related macular degeneration.

Signed: 

Bernie Murray
Inspector
Office of Environmental Sustainability