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:	**G0667-01**
SNIF Reference Number:	**B/IE/18/01**
GMO Notifier:	**uniQure Biopharma BV** **Paasheuvelweg 25A** **1105 BP Amsterdam** **The Netherlands**
Location of the Part B Deliberate Release:	**St James's Hospital** **James's Street** **Dublin 8**

Genetically Modified Organisms (Deliberate Release) Regulations, 2003
(S.I. No. 500 of 2003)

Decision of the Agency, under Article 18(5)(a) of the Genetically Modified Organisms (Deliberate Release) Regulations, 2003 (S.I. No. 500 of 2003).

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

Register of Genetically Modified Organisms (GMOs) Users in Ireland: G0667-01

SNIF Reference No: B/IE/18/01

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:

uniQure Biopharma BV
Paasheuvelweg 25A
1105 BP Amsterdam
The Netherlands

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

The administration of a recombinant adeno-associated virus (AAV5) based vector which has been designed to express human coagulation factor IX (AAV5-hFIXco-Padua) in patients with severe or moderately severe hemophilia B.

The aforementioned activity will be preformed in the following location:

St James's Hospital
James's Street
Dublin 8

The period of release extends from the date of grant of these consent conditions to 31st December 2021.

SEALED by the Seal of the Agency on this the 21st day of November 2018

PRESENT when the seal of the Agency was affixed hereto:

Tara Gillen

Tara Gillen
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:

uniQure Biopharma BV
Paasheuvelweg 25A
1105 BP Amsterdam
The Netherlands

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

St James's Hospital
James's Street
Dublin 8

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 and 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 factor IX deficiency.
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 within St James's Hospital where the deliberate release clinical trial will be carried out.
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 AAV5-hFIXco-Padua - a recombinant adeno-associated virus (AAV5) based vector which has been designed

	to express human coagulation factor IX (hFIX) in patients with severe or moderately severe hemophilia B. The GMO is also referred to as AMT-061.
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.
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 for Communications, Climate Action & Environment).
SOPs	Standard Operating Procedures

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Consent Conditions for GMO Register Entry No: G0667-01

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, St James's Hospital 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 December 2021:

St James's Hospital
James's Street
Dublin 8

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 December 2021. 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 St James's Hospital 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 preparation and administration of the GMO. It shall also include responsibility for monitoring of body fluids as described in the notification as well as the disposal and treatment of all GMO contaminated materials used during the course of the clinical trial.

4.3 Access to the storage area, clean room and day ward where the GMO will be stored, prepared and administered to the patient will be restricted to trained delegated staff.

4.4 The notifier shall provide the name and contact details of a person in the employ of uniQure Biopharma BV with responsibility for overseeing the performance of this clinical trial at St James's Hospital, James's Street, Dublin 8. These details shall be communicated to the Agency 2 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 The notifier shall provide the name and contact details of the PI and the Pharmacist with responsibility for the performance of this clinical trial to the Agency prior to the commencement of the clinical trial. Any change to this designation during the course of the trial shall be notified immediately to the Agency.

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

4.7 The notifier shall, prior to commencement of the clinical trial provide a copy of the agreement put in place with St James's Hospital describing the delegation of responsibility as required by Conditions 4.1 and 4.2.

4.8 Personnel involved in performing specifically assigned tasks shall be:

4.8.1 made aware of risks relating to the GMO associated with the trial;
4.8.2 made aware of possible routes of exposure to the GMO and the procedures to follow in the event of accidental exposure.

4.9 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 concerned:

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/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 Personal Protective Equipment

6.2.1 Personnel preparing the GMO for patient administration or administering the GMO to the patient or in attendance for purposes of verification against the clinical trial protocol, will be required to wear suitable protective clothing, including gown, gloves, safety glasses and mask and any other protective clothing as may be deemed necessary by the notifier.

6.2.2 Gowns and other protective clothing shall be worn only in the work area and removed before leaving it.

6.3 Storage

6.3.1 The GMO shall be stored separately and securely in a designated freezer within the facility at St James's Hospital, Dublin 8.

6.3.2 Access to the GMO freezer shall be limited to designated staff.

6.3.3 The notifier shall maintain a record of the dates of receipt of the GMO, batch numbers (if relevant), the volume of GMO received and the date of removal from the freezer for preparation for patient administration.

6.4 Transport

6.4.1 The GMO shall be transported within secondary containment (sealed, leakproof and unbreakable container with appropriate

labelling) within the facility to minimise the potential for spillage and the container shall be opened within a pharmaceutical isolator.

6.5 Preparation of the GMO for administration

6.5.1 Preparation of the GMO for patient administration shall take place within a pharmaceutical isolator within a clean room by a trained pharmacist using aseptic technique.

6.5.2 The isolator shall be decontaminated after use using a viricidal disinfectant that is known to effectively destroy Adeno Associated Virus (AAV). The manufacturer's instructions shall be adhered to.

6.6 Administration of the GMO

6.6.1 Personnel involved in the administration of the GMO shall be familiar with the clinical trial risk assessment as well as with procedures that minimise exposure of the GMO to themselves and to the environment.

6.7 Standard Operating Procedures (SOPs)

6.7.1 Prior to the date of 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 with disinfectants;
- Cleaning and disinfection of non-disposable equipment;
- Validation, servicing, control and maintenance of containment 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.

6.7.2 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.

6.7.3 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, their positions and their deputies responsible for the conduct of this clinical trial, their tasks and responsibilities. This list shall be made available to the Agency on request.

7.2 All persons with access to the work area where the clinical trial will be carried out shall be informed about the nature of the clinical trial.

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. 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 materials contaminated with the GMOs shall be disposed into appropriately labelled, closed, unbreakable, leak-proof containers while awaiting collection by an authorised waste contractor. Waste storage containers shall display biohazard signs.

8.2 GMM contaminated sharps waste shall be disposed of into sharps bins.

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

8.4 GMM contaminated waste shall be collected by a waste contractor authorised under the GMO (Contained Use) Regulations (2001 to 2010) 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.

8.5 The notifier shall obtain and maintain GMM waste inactivation records. These 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

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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.

9.2 The notifier shall inform the Agency in writing of the date of commencement of the clinical trial no later than 2 weeks prior to its commencement.

9.3 Reports to the Agency on the results of the clinical trial:

9.3.1 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 June 2022. This report shall include the following information:

- the results of the deliberate release;
- 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 St James's Hospital 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 St James's Hospital with responsibility for these records/reports.

9.5 On completion of the clinical trial, the notifier shall notify the Agency in writing. The notifier shall verify in writing that no GM material relating to this trial is stored in the St James's Hospital facility.

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**

[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)

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 a person in the employ of uniQure Biopharma BV with responsibility for overseeing the performance of this clinical trial at St James's Hospital, James's Street, Dublin 8 (Condition 4.3). Any change to this designation shall be notified to the Agency immediately, (Condition 4.3)	Notifier shall make available to clinical trial staff: • SOPs set out under Condition 6.7.1 (Condition 6.7.) • SOP on worker protection measures (Condition 7.3)
	Notifier Date of trial commencement (Condition 9.2)	
To be provided prior to trial commencement	Notifier A copy of the agreement put in place with St James's Hospital describing the delegation of responsibility, (Condition 4.7)	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
	Notifier Provide the name and contact details of the PI and the Pharmacist (i.e. telephone number, and e-mail address) (Condition 4.5)	
	Notifier Shall implement SOPs set out under Condition 6.7.1	
	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 6.7.1 (Condition 6.7.2)	
	List of all positions, persons and their deputies responsible for conduct of the clinical trial (Condition 7.1)	
	GMM waste inactivation records (Condition 7.3.1)	

	Training records (Condition 9.6)	
to be provided to the Agency on trial completion	Notifier • Notification of trial completion (Condition 9.5) • Report in the format set out under Commission Decision 2003/701/EC (Condition 9.3)	

Annex II

Principles of good microbiological practice and good occupational safety and hygiene practice shall include:

(i) keeping the workplace and environmental exposure to any genetically modified micro-organism to the lowest practicable level;

(ii) exercising engineering control measures at source and where necessary supplementing these with appropriate personal protective clothing and equipment;

(iii) testing and maintaining control measures and equipment;

(iv) testing where necessary for the presence of viable process organisms outside the primary physical containment;

(v) providing appropriate training of personnel;

(vi) establishing biological safety committees or subcommittees where required;

(vii) formulating and implementing local codes of practice for the safety of personnel where required;

(viii) where appropriate displaying biohazard signs;

(ix) providing washing and decontamination facilities for personnel;

(x) keeping adequate records;

(xi) prohibiting eating, drinking, smoking, applying cosmetics or the storing of food for human consumption in the work area;

(xii) prohibiting mouth pipetting;

(xiii) where appropriate, providing written standard operating procedures to ensure safety;

(xiv) having effective disinfectants and specified disinfection procedures available in the case of spillage of genetically modified micro-organisms and;

(xv) where appropriate, providing safe storage for contaminated laboratory equipment and materials.

Annex III

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 21st day of November 2018.

PRESENT when the seal of the Agency was affixed hereto:

Tara Gillen

Tara Gillen
Authorised Person