Cleared by David Flynn for
submission to the Director.

Teresa Roche 7 November 2018
Teresa Roche

Office of Environmental Sustainability

INSPECTOR'S REPORT

TO:	BOARD OF DIRECTORS
FROM:	Bernie Murray - Environmental Licensing Programme
DATE:	7 November 2018
RE:	Notification from uniQure Biopharma BV, Paasheuvelweg 25A, 1105 BP Amsterdam, Netherlands 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: G0667-01).

Applicant:	uniQure Biopharma BV Paasheuvelweg 25A 1105 BP Amsterdam The Netherlands		
GMO Register Entry No:	G0667-01		
SNIF No[1]:	B/IE/18/01		
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:	28/06/2018		
Request for additional information under Article 19 of S.I. 500 of 2003:	31/08/2018	14/09/2018	17/10/2018
Additional Information submitted under Article 19 of S.I. 500 of 2003:	10/09/2018	06/10/2018	01/11/2018
Date by which decision is required:	08/11/2018		

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

Representations to the EPA relating to this notification under Article 16 of S.I. 500 of 2003:	0

Introduction

uniQure Biopharma BV, Paasheuvelweg 25A, 1105 BP Amsterdam, Netherlands sought the consent of the Environmental Protection Agency (EPA) on 28 June 2018 to perform a Phase III clinical trial investigating AMT-061.

AMT-061 is a gene therapy that uses a recombinant serotype 5 adeno-associated viral (AAV5) vector carrying the gene for a mutated factor IX (FIX) called the Padua variant (FIX-Padua). FIX is an important clotting protein that is deficient in patients with hemophilia B. AMT-061 will be administered to adult patients with severe or moderately severe haemophilia B and it is expected that it will give rise to a higher production of FIX.

The purpose of the work is to further establish an AAV-based, liver directed gene therapy approach for the treatment of haemophilia B, while assessing the safety and efficacy of a single dose delivery method.

It is proposed that this trial will be carried out in the in St James's Hospital, James's Street, Dublin 8. The notification was submitted by the notifier (uniQure Biopharma BV) in accordance with Part II of the GMO (Deliberate Release) Regulations (S.I. 500 of 2003).

Haemophilia B is a predisposition to bleeding caused by a deficiency of blood coagulation factor IX (9) (FIX). Haemophilia occurs mostly in men (affecting 1 in 30,000 males worldwide) of which the majority suffer from severe (FIX activity ≤1% of normal) or moderately severe (FIX activity ≤2% of normal) disease. The population prevalence of haemophilia B in Ireland is 1 per 12,500 males which is higher than the observed prevalence worldwide.

There is no cure for haemophilia B. Current treatment for the condition involves injections of commercially available recombinant, or plasma-derived FIX products either at the time of the bleed (on-demand) or by regular infusions up to several times a week (prophylactically). Without such treatments patients, may experience frequent painful bleeding events into joints and muscles. Over time with repeated bleeds patients may develop irreversible, debilitating joint damage resulting in lifelong pain with reduced mobility and function.

Recent scientific advances have resulted in gene therapy treatments which have been able to shift the disease severity from severe to moderate.

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 and 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 have considered:

- the patient receiving the treatment insofar as they are part of the general population and 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), AMT-061, is a recombinant serotype 5 adeno-associated viral vector containing the Padua variant of a codon optimised human factor IX gene (AAV5-hFIXco-Padua).

Purpose of the proposed deliberate release

The purpose of the proposed trial is to further establish an AAV-based, liver directed gene therapy approach for the treatment of haemophilia B, while assessing the safety and efficacy of the administration of a single dose of AMT-061 to adult patients.

Proposed location of the deliberate releases

The proposed deliberate release will take place at the St James's Hospital, James's Street, Dublin 8.

Timeframe for the proposed clinical trial

This proposed trial will take place during the period January 2019 – December 2021. It is estimated that approximately two to five patients will be treated in Ireland.

The Notifier

The notifier and trial sponsor, uniQure Biopharma B.V., is located in the Netherlands. It has already carried out a Phase II clinical trial involving AMT-061 and proposes to carry out Phase III trials in Belgium, Germany, Denmark, Spain, Finland, France, UK, Italy, Sweden and Ireland. An application in respect of a Phase III clinical trial involving AMT-061 has already been submitted to the competent authority in the Netherlands.

A Principal Investigator (PI) located in St James's Hospital will be responsible for the conduct of the clinical trial including oversight of individuals to whom tasks will be delegated. The chief Pharmacist will be responsible for receipt and preparation of the GMO. The PI will have responsibility for the administration of the GMO to the patient.

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 not located in Ireland 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 St James's Hospital) nor St James's Hospital will bear any responsibility to the EPA to ensure compliance with the consent. Legal advice sought by ELP in this regard has indicated that while there are practical difficulties in terms of enforcement, it is not a bar to granting consent.

Environmental Risk Assessment

The notifier conducted a risk assessment in accordance with Article 5(2) and the Second Schedule of the GMO (Deliberate Release) Regulations, S.I. No 500 of 2003.

The GMO is a DNA virus assembled from molecular components of adeno associated virus serotype 5 (AAV5) and adeno associated virus serotype 2 (AAV2) and engineered with human factor IX. It is attenuated: it does not contain any of the AAV genes that are essential for the replication of viral DNA, the formation of viral particles or the packaging of viral DNA into these particles.

Wild-type AAV (wtAAV) is frequently found in humans and can infect animals but it is not pathogenic, toxigenic, virulent, allergenic or a carrier of a pathogen.

Recombinant AAV based vectors are usually classified as Class 1 activities. AAV needs a helper virus such as adenovirus or herpes virus to replicate. The wtAAV genome carries two genes for capsid formation (Cap) and DNA replication and packaging (Rep). The AMT-061 vector genome does not contain the Rep and Cap genes. Thus, AMT-061 is replication-defective, even in the presence of a helper virus.

The recombinant AAV based vector carries a transgene expression cassette containing the human Padua factor IX transgene (which is a naturally occurring sequence in humans) in addition to other individual molecular components which play a role in transgene expression. The hFIX-Padua sequence is codon optimised to enhance protein expression.

Following administration of AMT-061 to patients, it is expected to preferentially localise to the liver where it will infect and transduce liver tissue. hFIX-Padua will be expressed and excreted into the circulation at activity levels eight to nine times greater than normal. The vector DNA is expected to persist in liver cells and provide sustained therapeutic clotting factor levels.

AMT-061 is infectious in that it must infect the patient's liver cells in order for AMT-061 to express the transgene. Infectious particles can only be found in blood during the first three days after vector infusion following which they are cleared from the circulation having been taken up by the patient's liver cells or having been rendered non-infectious through degradation by the patient's own immunity.

Shedding

Due to the above, spread of infectious GMO into the environment through nasal secretions, saliva, urine or faeces is considered negligible as shed material will contain DNA fragments of the GMO or vector DNA which is non-infectious. Vector DNA is expected to shed through blood, urine, saliva, faeces and semen for several

days after administration. Concentrations of infectious AMT-061 contained in these body fluids is low and even if shed, AMT-061 lacks Rep and Cap genes making it replication incompetent and thereby limiting any potential spread.

Spread of infectious GMO through blood is conceivable as blood samples are drawn during the first three days after administration of the GMO. Persons working with the GMO could come into contact with it at this time through, for example, accidental injection during administration. Any ensuing effects – immune response and marginal increase in FIX levels - will not affect the recipient's wellbeing.

Immune response

Administration of the GMO will elicit an immune response to AAV very similar to natural infection with wtAAV. No immune response will be elicited to the expressed transgene.

Recombination

Recombination is theoretically conceivable but deemed unlikely. It would require simultaneous infection of one-and-the-same cell with AAV5-hFIX, wtAAV and a helper virus which in itself is deemed unlikely. Replication competent AMT-061 particles would not be formed. Recombinant replication deficient particles could theoretically be formed but they would carry the same characteristics as AMT-061 and wtAAV. The risk associated with recombination is considered to be negligible.

Since AMT-061 contains the ITR-sequences of AAV2, there is a (remote) possibility of homologous recombination of the vector with wtAAV2 in case of a co-infection in exposed persons. The result of such a recombination would be that AMT-061 would gain functional genes of the AAV2 required for replication and encapsidation, but in turn would lose the transgene. Hence, recombination would lead to the formation of viruses that are identical to the starting material and are replication incompetent.

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 transgenes.

Risks to the Environment

Wild type AAV is not known to be involved in environmental processes.

Due to the extremely low numbers of AMT-061 particles potentially released into the environment during the study, either by accident or through shedding, horizontal gene transfer is unlikely. Even if horizontal gene transfer occurred, AMT-061 sequences would not confer a selective advantage to bacteria: AMT-061 does not contain any prokaryotic promoters, any antibiotic or other types of resistance genes or any genes which would enhance or constrain their growth. Therefore, it is unlikely that the vector would interfere with the control of pathogenic microorganisms or that it would have an effect on the natural dynamics of microbial populations or the biogeochemical cycles at any given site in the environment.

Storage, preparation and administration of the vector

The GMO will be shipped to St James's Hospital on a patient-by-patient basis following confirmation of a patient's suitability to participate in the trial. The precise amount of AMT-061 to be administered to the patient will arrive in the facility on dry ice, approximately 7 days prior to the planned administration date. It will be stored in a dedicated -65^{o}C freezer located in a restricted swipe access pharmacy room. The freezer is linked to a dedicated freezer alarm to ensure temperature stability. Storage is not expected to exceed 14 days, however, in the event of unforeseen circumstances, the GMO may be stored for up to 12 months at -65^{o}C.

Vials containing AMT-061 will be thawed at room temperature and diluted prior to use, by the Pharmacist. The GMO will be administered as a single dose. 2 x 10^{13} gc/kg (the dose will be dependent on the weight of the patient) will be diluted in a 500ml 0.9% saline infusion bag and administered intravenously to the patient by a Consultant and Nurse over a period of one hour.

Worker protection measures taken during the release

Dilution of the GMO will be performed under aseptic conditions in a dedicated pharmaceutical isolator (condition 6.5) which maintains a Grade A Good Manufacturing Practice (GMP) environment. This is a closed system under negative air pressure and the extract air is HEPA filtered. It ensures that the concentrate AMT-061 does not come into contact with the environment. Furthermore, the potential for a needle stick injury to occur is negligible. The pharmaceutical isolator will be contained in a clean room (under positive air pressure) which will operate at Grade D GMP and access to the clean room is restricted to pharmacy staff.

Intravenous administration of the GMO will take place in a day ward next door to the clean room. Access to the day ward is swipe card restricted. The administering Consultant/Nurse will wear personal protective clothing such as a theatre gown, face mask, gloves and glasses (condition 6.2). During preparation of the GMO for patient administration, the pharmacist will, in addition to the above, wear a mob cap and overshoes.

Known pregnant women will not be assigned to administer the GMO.

Access to the facility will be restricted to trained delegated staff (condition 4.3) (PI Consultant, Consultant back-up, Nurse, Nurse back-up, Pharmacy staff). Prior to the commencement of the trial, staff training will be provided by uniQure Biopharma BV.

Condition 6.7 and 7.3 requires the implementation of SOPs relating to the handling of the GMO within the facility and worker protection measures respectively.

Waste production, treatment and disposal

uniQure Biopharma BV will supply spill kits to the facility to be made available during all the steps involving AMT-061 (storage, preparation and administration) to counteract spillage and/or aerosol formation.

All sharps waste (vial, infusion bag and line and patient cannula) will be disposed of in a sharps bins. There will be a designated sharps container for blood waste.

There will be two 20L yellow bins for GMO waste - one in the ante room to the clean room for the waste from GMO preparation and one in the treatment room for the waste from patient administration. These bins can be closed and transferred to one 60L bin or a 60L bin in each area. All sharps bins will be stored in the 60L capacity biohazard bins along with contaminated non-sharp solid waste (PPE, cleaning pads, wipes). The 60L biohazard bins will be removed by SRCL Ltd (G0063-01 and W0054-02) and exported to England for incineration.

Condition 8 requires that bins are labelled, display biohazard signs, are unbreakable and leakproof. In addition, the notifier is required to obtain GMM waste inactivation records and retain these records at St James's Hospital to be made available to the Agency on request (condition 9.4).

Duration and frequency of monitoring

Treated patients will be retained for approximately 3 hours for purposes of observation before being discharged. The patient is required to return to the facility weekly for the first 12 weeks and monthly from month 4 to 12 for purposes of monitoring body fluids (serum and semen). Body fluids will be monitored for the presence of vector DNA until three consecutive samples are reported negative.

Body fluid samples will be sent to the national coagulation lab in St James's Hospital for centrifugation before forwarding to the central pathology lab in Belgium for central lab analysis. Staff in the national coagulation lab are trained in handling samples from haemophiliac patients.

No specific laboratory work will be conducted in St James's Hospital facility, rather AMT-061 will be stored, prepared and administered to the patient within the facility.

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 "Dublin Gazette" newspaper (circulating in the area of St James's Hospital) on 5th July 2018, and the period for submission of representations ended on 2nd August 2018. 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 5 replies none of which expressed any concern provided all procedures are followed as stated in the Environmental Risk Assessment

Consultation with other regulatory bodies and government departments

A separate application was submitted to the Health Products Regulatory Authority (HPRA) by uniQure under Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. The proposed clinical trial was approved by the HPRA in July 2018.

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 (03/08/2018). The Agency did not receive any comments or observations from other member states.

Internal review

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

Site Inspection

A site inspection of the St James's Hospital facility was carried out on 31 October 2018 during which I met with the chief Pharmacist, the PI and the Nurse all of whom will be part of the trained and delegated staff with responsibility for the performance of this proposed trial. The life cycle of the GMO from its receipt at the facility, storage prior to use, preparation and patient administration and disposal of GM contaminated material were addressed during the site inspection. The necessary facilities for GMO storage (-65^{o}C freezer) and preparation of the GMO for patient administration (pharmaceutical isolator) are in the process of being finalised. The containment measures that are being applied by the notifier in many instances exceed the requirements for a Class 1 GMM under the GMO (Contained Use) Regulations, 2001 to 2010. The trial will also be carried out in accordance with Good Clinical Practice guidelines.

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 of the mandatory information.

AMT-061 is a recombinant, replication-deficient, AAV-based vector that will be administered to severe or moderately severe haemophilia B patients. 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. Delegated hospital staff will be trained by the notifier in biosafety practices and the safe handling of GMOs.

The overall risk of AMT-061 to people and the environment can be considered negligible.

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

I am satisfied on the basis of the review carried out that the risks posed to the environment and human health (general population) by the deliberate release of this GMO are negligible.

On this basis I recommend that consent be granted, subject to conditions, to UniQure Biopharma BV, Paasheuvelweg 25A, 1105 BP Amsterdam, Netherlands for the deliberate release of AMT-061, during a clinical trial under Part B of the GMO (Deliberate Release) Regulations, S.I. No 500 of 2003 at St James's Hospital, Dublin 8. The clinical trial will assess the safety and efficacy of the administration of a single dose of AMT-061 to adult patients with severe or moderately severe haemophilia B who meet study inclusion criteria.

Signed: 

Bernie Murray
Inspector
Office of Environmental Sustainability