[redacted]

From: Bernadette Murray
Sent: 31 August 2018 16:02
[redacted]@[redacted]
Subject: request for further information relating to G0667-0 (B/IE/01/18)

[redacted]

Further to our telephone conversation yesterday afternoon, enclosed please find a request for further information relating to G0667-0 (B/IE/01/18)
in accordance with Article 19(1) of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003

Incidentally the SNIF was published by the JRC on 3rd August 2018 and the Agency received no representations in response to your newspaper advert.

I would be grateful if you would forward details for the BSO at the earliest opportunity so that I can liaise with him/her and arrange a visit please.

Please email me if you need clarity on any of these issues.

Regards
Bernie

Bernie Murray
Environmental Protection Agency
P.O. Box 3000
Johnstown Castle Estate
Co Wexford
IRELAND

+353 53 9167252
b.murray@epa.ie

G0667-01, uniQure Biopharma B.V., Deliberate Release Clinical Trial
Request for further information in accordance with Article 19(1) of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003

Newspaper Notice

1. In what area of Dublin is the Dublin Gazette newspaper circulated?

Haemophilia B

2. What is the prevalence of Haemophilia B in Ireland?
3. How is the condition currently treated?

Trial Location / Principle Investigator (PI) / Responsibility

4. Where in St James's Hospital (section / department) will this trial be carried out?
5. Please provide details of the PI (name, department).
6. What is the role of the PI in the performance of this trial?
7. Who ultimately does responsibility for the performance of this trial rest with?
8. Who will be responsible for receipt of the GMO, preparation and administration of the GMO to the patient?

Storage

9. Please specify the maximum period for which the GMO will be stored (at ≤-65°C) prior to use and the location of the freezer relative to the treatment room.
10. What is the volume of each vial and what volume of GMO will be administered to the patient?

Decontamination

11. Please specify how all GMM contaminated solid waste (including open vials, remaining product) and all GMM contaminated liquid waste (including any remaining product) will be treated before disposal.
12. Please clarify whether unused (unopened) vials of AMT-061 will be destroyed or returned to the sponsor (section 4.4.7)?
13. Please specify how spillages (all types) will be treated. Where applicable specify the type of disinfectant that will be used and the concentration thereof?
14. Where an autoclave will be used for purposes of decontamination, provide details of
    - the cycle parameters (time temperature pressure);
    - its location in relation to the rooms where preparation and administration of the GMO will take place;
    - date on which the autoclave was last validated.

Other

15. Part 1.F. 4 (c) states that the investigational medicinal product will be supplied ... .. on a 'subject to subject' basis. I understand that the product will be supplied after the suitability of the patient has been confirmed but aside from that what is meant by 'subject to subject'?

16. There appears to be a few different terms in use. Please clarify
    - AMT-061 is not infectious after being shed (4.4.9) as it will predominantly contain only DNA fragments of the GMO and is unlikely to contain infectious particles (4.5.2).
    - AAV-based GMO found in body fluids is not infectious except in the blood where it can be infectious for up to 3 days after administration (4.5.1)
    - Vector DNA (SNIF H.5 – body fluids of treated patients will be monitored until found negative for the presence of vector DNA)
    - AMT-061 derived DNA.

- infectious vector particles – Section 4.1.4 states *In the unlikely event that infectious particles will be shed, these will still be replication-deficient due to the vector design and manufacturing strategy. Shedding of vector material may lead to exposure of third parties which theoretically may result in transmission to these third parties.*

Please clarify these different terms. Why are these particles described as 'infectious' or as having the capacity to spread if they do not have the capacity to replicate. What does 'infectious' mean / refer to and what is the infectious element?

If AMT-061 does not contain Rep and Cap genes and is replication defective as a consequence (even in the presence of a helper virus) then why or how can it be infectious in the blood for up to 3 days after administration.

17. Section 4.1.5 relates to recombination and states that in order for AMT-061 to revert to replication competent AAV, triple co-infection of the same cell with AMT-061, wtAAV and helper virus would be required. This is deemed to be unlikely yet section 4.1.2 states that infections with AAV occurs frequently and worldwide. Therefore it would seem that the likelihood of triple co-infection of the same cell could be substantial?

18. What risk (if any) will the GMO present to immunocompromised persons / pregnant women who may come into contact with it during preparation / administration of the GMO

19. Please forward a copy of correspondence sent to the CEO of St James's Hospital (Mr Lorcan Birthistle) and to the Chief Executive of Dublin City Council (Mr Owen Keegan) in accordance with Article 15(3) of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003.

Teresa Roche

From: [redacted]
Sent: 10 September 2018 11:54
To: Bernadette Murray
Cc: Licensing Staff; Teresa Roche
Subject: CT-AMT-061-request for further information relating to G0667-0 (B/IE/01/18)
Attachments: Request for additional information1_01092018.docx; G0667-01-response to request for additional information-CT-AMT-061-10sept2018.zip

Importance: High

Dear Bernie

Please find attached the information requested to progress the GMO submission assessment for the clinical study mentioned above.

Sincerely

[redacted]

[redacted]

[redacted]

From: Bernadette Murray <B.Murray@epa.ie>
Sent: 31 August 2018 16:02
[redacted]
Subject: request for further information relating to G0667-0 (B/IE/01/18)

Dear [redacted]

Further to our telephone conversation yesterday afternoon, enclosed please find a request for further information relating to G0667-0 (B/IE/01/18)
in accordance with Article 19(1) of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003

Incidentally the SNIF was published by the JRC on 3rd August 2018 and the Agency received no representations in response to your newspaper advert.

I would be grateful if you would forward details for the BSO at the earliest opportunity so that I can liaise with him/her and arrange a visit please.

Please email me if you need clarity on any of these issues.

Regards
Bernie

Bernie Murray
Environmental Protection Agency
P.O. Box 3000
Johnstown Castle Estate
Co Wexford
IRELAND

+353 53 9167252
b.murray@epa.ie

[redacted]

Please consider the environment when printing this email.

Environmental Protection Agency
Office of Environmental Sustainability
P.O. Box 3000
Johnstown Castle Estate
Co Wexford
IRELAND

Submission by email to: licensing@epa.ie
cc: b.murray@epa.ie; and T.Roche@epa.ie

10 September 2018

G0667-01, uniQure Biopharma B.V., Deliberate Release Clinical Trial

Response to Request for further information
(in accordance with Article 19(1) of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003)

Protocol Title:	Phase III, open-label, single-dose, multi-centre multinational trial investigating a serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIXco-Padua, AMT-061) administered to adult subjects with severe or moderately-severe hemophilia B
Protocol ID:	CT-AMT-061-02
IMP:	AAV5-hFIXco-Padua (serotype 5 adeno-associated viral vector containing a codon optimised human factor IX Padua gene)
EPA reference	G0667-01

Dear Dr Murray

Please find below the information requested to progress the GMO submission assessment for the clinical study mentioned above. Please note all communications to arrange a site visit should be directed to the Principal Investigator (PI) and to the clinical research co-ordinator (CRC) at:

Email: NOConnell@ stjames.ie (Dr O'Connell, the PI)
Email: MaNolan@stjames.ie (for Margaret Nolan, the CRC)

1. EPA request

Newspaper Notice
In what area of Dublin is the Dublin Gazette newspaper circulated?

Sponsor response
The Dublin Gazette is circulated in Dublin City and County (Dublin Gazette South Edition, North Edition, West Edition and City Edition). Please see the Dublin Gazette distribution map enclosed.

The public notice for the clinical trial mentioned above was advertised in the Dublin Gazette-City Edition, which is distributed in the areas of the trial site (St. James's Hospital) and of the Dublin City Council.

[redacted]

2. **EPA request**

Haemophilia B
What is the prevalence of Haemophilia B in Ireland?

Sponsor response
Haemophilia B generally arises as a result of unique mutations within the F9 gene and occurs with a prevalence of approximately one case per 30 000 males worldwide. The population prevalence of haemophilia B in Ireland at one per 12 500 males is higher than the observed prevalence worldwide, likely due to a founder effect as opposed to de novo F9 mutations (Jenkins et al., 2008)

Reference:
Jenkins PV, Egan H, Keenan C, O'Shea E, Smith OP, Nolan B, White B, O'Donnell J (2008) Mutation analysis of haemophilia B in the Irish population: increased prevalence caused by founder effect. Haemophilia. Jul;14(4):717-22. doi: 10.1111/j.1365-2516.2008.01765.x. Epub 2008 May 7

3. **EPA request**

Haemophilia B
How is the condition currently treated?

Sponsor response
There is no cure for haemophilia B. The primary goals of haemophilia B therapy are the prevention of bleeding episodes, rapid and definitive treatment of bleeding episodes (breakthrough bleeds) that occur even while on a regular prophylactic regimen and provision of adequate hemostasis during surgery and emergencies. Currently, these goals are essentially met for haemophilia B subjects by intravenous injections of commercially available recombinant- or plasma-derived FIX products, either at the time of a bleed (on-demand) or by regular infusions up to several times a week (prophylactically). The recent approvals of extended half-life FIX products allow for reduced frequency of factor administration (once every 7 to 14 days) and maintaining a higher FIX trough level (Taylor and Kruse-Jarres, 2016).

Reference:
Taylor JA, Kruse-Jarres R (2016) A new era for hemophilia B treatment. Blood. 127(14): 1734-1736

4. **EPA request**

Trial Location / Principle Investigator (PI) / Responsibility
Where in St James's Hospital (section / department) will this trial be carried out?

Sponsor response
The clinical trial will be carried out at the Clinical Research Facility, 2nd Floor H&H Building, St James's Hospital, James's Street, Dublin, D08A978

5. **EPA request**

Trial Location / Principle Investigator (PI) / Responsibility
Please provide details of the PI (name, department).

[redacted]

Sponsor response
The PI for the study is Dr Niamh O Connell
Department: National Coagulation Centre, St James's Hospital, Dublin

6. EPA request

Trial Location / Principle Investigator (PI) / Responsibility
What is the role of the PI in the performance of this trial?

Sponsor response
The role of the PI is to be responsible for the conduct of the clinical trial in accordance with ICH GCP, including oversight of individuals delegated to tasks within the clinical trial protocol.

7. EPA request

Trial Location / Principle Investigator (PI) / Responsibility
Who ultimately does responsibility for the performance of this trial rest with?

Sponsor response
The PI has overall responsibility for conduct of the clinical trial, in accordance with the trial protocol and the requirements of ICH-GCP.

8. EPA request

Trial Location / Principle Investigator (PI) / Responsibility
Who will be responsible for receipt of the GMO, preparation and administration of the GMO to the patient?

Sponsor response
The chief Pharmacist will be responsible for receipt and preparation of the GMO.
The principle investigator will have overall responsibility for administration of the GMO to the patient.

9. EPA request

Storage
Please specify the maximum period for which the GMO will be stored (at ≤-65°C) prior to use and the location of the freezer relative to the treatment room.

Sponsor response
The GMO is expected to arrive at the site approximately 7 calendars prior to the planned administration date. Routine storage at <-65degC of the GMO for more than 14 calendar days is not expected. In the event of unforeseen circumstances, the GMO may be stored for a period up to the expiry date (i.e. up to 12 months at <-65degC).

The location of the freezer relative to the treatment room is shown on the floor plan enclosed. The distance between the freezer and the treatment room is ~25 m.

[redacted]

10. EPA request

Storage
What is the volume of each vial and what volume of GMO will be administered to the patient?

Sponsor response
Each vial contains 10.0 mL of the GMO.

The volume of the GMO to be imported into Ireland is dependent on the weight of the patient to be treated (patients will be dosed with 2×10^{13} gc/kg). It is estimated that approximately 5 patients will be treated in Ireland and that each patient will require 18 x 10mL vials of GMO.

11. EPA request

Decontamination
Please specify how all GMM contaminated solid waste (including open vials, remaining product) and all GMM contaminated liquid waste (including any remaining product) will be treated before disposal.

Sponsor response
Waste will be treated as per hospital waste management policy for Biological/ Infectious Waste (policy enclosed). Waste will be collected and incinerated as per central hospital contract in line with local procedures. The Sponsor recommends incineration of waste without autoclaving provided the contaminated waste is packaged in such a way so as not to be exposed to the environment (for example the waste will be placed in a sealed plastic bag or container until incineration).

All sharp clinical waste will be disposed into clinical waste sharp bins for incineration. Contaminated liquid waste will be disposed into rigid waste containers for incineration. All contaminated non-sharp solid waste is collected into a clinical waste bag for incineration.

Any residual viral construct stocks will be disposed into clinical waste sharp bins for incineration. All thawed (used and unused) vials involved in the preparation and administration of AMT-061 will be disposed of as soon as possible after a second person from the site has verified the accountability or pictures have been taken of the used and unused vials. Destruction occurs in accordance with local hospital procedures and biohazard standards of law.

In the event that there is a complete, unused AMT-061 Patient Pack that will not be used at the site, written confirmation will be provided and filed and destruction records will be collected.
After use, any disposable supplies used in the preparation of the AMT-061 infusate or in the AMT-061 infusion will be discarded in hazardous waste bins and the bin number recorded.

All waste bags and containers are to be transported from clinical area to waste collection bin location in robust closed leak proof containers.

12. EPA request

Decontamination
Please clarify whether unused (unopened) vials of AMT-061 will be destroyed or returned to the sponsor (section 4.4.7)?

[redacted]

Sponsor response
Unused vials will be destroyed on site in accordance with local hospital procedures and biohazard standards of law (see response to Q11 for more details).

13. EPA request

Decontamination
Please specify how spillages (all types) will be treated. Where applicable specify the type of disinfectant that will be used and the concentration thereof?

Sponsor response
Spills kits / wipes to be used in case of spillages and staff must follow the instructions given by the manufacturer. In case of spillage the affected area, lineated with absorbing material, will be decontaminated using appropriate disinfectants with virucidal activity (e.g. Klercide Sporicidal Active Chlorine disinfectant, please see literature enclosed). A spill kit will be available at all times during the administration procedure. The instructions for what to include in the spill kit will be sent to the site with the IMP shipment.

14. EPA request

Decontamination
Where an autoclave will be used for purposes of decontamination, provide details of

- the cycle parameters (time temperature pressure);
- its location in relation to the rooms where preparation and administration of the GMO will take place;
- date on which the autoclave was last validated.

Sponsor response
Waste will be collected and incinerated as per central hospital contract. Waste will not be autoclaved.

15. EPA request

Other
Part 1.F. 4 (c) states that the investigational medicinal product will be supplied ... on a 'subject to subject' basis. I understand that the product will be supplied after the suitability of the patient has been confirmed but aside from that what is meant by 'subject to subject'?

Sponsor response
The product will be supplied after the suitability of the patient has been confirmed. The product will be provided for that specific patient ("subject-to-subject" basis) with the required number of vials (based on the patient's weight) kitted into a patient specific tamper resistant sealed kit (box).

16. EPA request

Other
There appears to be a few different terms in use. Please clarify

- AMT-061 is not infectious after being shed (4.4.9) as it will predominantly contain only DNA fragments of the GMO and is unlikely to contain infectious particles (4.5.2).

[redacted]

- AAV-based GMO found in body fluids is not infectious except in the blood where it can be infectious for up to 3 days after administration (4.5.1)
- Vector DNA (SNIF H.5 – body fluids of treated patients will be monitored until found negative for the presence of vector DNA)
- AMT-061 derived DNA.
- infectious vector particles – Section 4.1.4 states In the unlikely event that infectious particles will be shed, these will still be replication-deficient due to the vector design and manufacturing strategy. Shedding of vector material may lead to exposure of third parties which theoretically may result in transmission to these third parties.

Please clarify these different terms. Why are these particles described as 'infectious' or as having the capacity to spread if they do not have the capacity to replicate. What does 'infectious' mean / refer to and what is the infectious element?

If AMT-061 does not contain Rep and Cap genes and is replication defective as a consequence (even in the presence of a helper virus) then why or how can it be infectious in the blood for up to 3 days after administration.

Sponsor response
Theoretically shedding of infectious particles cannot be excluded. We understand that the wording in 4.4.9. "AMT-061 is not infectious after being shed" is somewhat confusing. What should have been indicated is that infectious AMT-061 may be present but that these vector particles will remain replication defective considering the deletion of Rep and Cap genes.

As described in 4.3, shed vector DNA does not equal infectious vector particles. It has been described that infectious particles can only be found in blood during the first 3 days after vector infusion (Favre et al., 2001). After this period all infectious particles are likely to have infected test subject cells or to have been rendered non-infectious through other mechanisms (e.g. degradation by test subject effector mechanisms). The level of risk that spread will actually occur is therefore dependent of the scenario, i.e. fluid or excrement type.

Due to the above, spread of infectious GMO into the environment through nasal secretions, saliva, urine or faeces is considered negligible. Spread of infectious GMO through blood is conceivable as blood samples are drawn during the first 3 days after administration of the GMO. However, following the worst-case scenarios described in the section: Exposure at the administration site, even the risk that AMT-061 will spread into the environment through blood and thus lead to a GMO related risk is considered negligible. Therefore the conclusion in 4.4.9 that standard hospital hygiene measures are sufficient and no additional measures will be taken after IMP administration is still valid.

Monitoring of body fluids until found negative as indicated in the SNIF is performed following the requirement of other GMO authorities in different countries where the study will be initiated. It should be indicated that given the environmental risk assessment outcomes this monitoring would not be strictly required as a "risk management" procedure.

AMT-061 derived DNA refers to DNA fragments containing degraded parts of the AMT-061 genome. These parts may be present in shedding compartments but will not be infectious as infectious AMT-061 is defined as being an AAV capsid containing the complete vector genome. As the AMT-061 vector genome does not contain AAV Rep and Cap genes rendering it replication deficient transmission to third parties when this would shed theoretically could occur but following the worst case scenario's as described is considered to be a negligible risk. Replication deficiency should not be mixed up with infectivity. AMT-061 is infective as infection of the test subject cells is required in order for AMT-061 to express its transgene. When following administration shedding

[redacted]

19. EPA request

Other

Please forward a copy of correspondence sent to the CEO of St James's Hospital (Mr Lorcan Birthistle) and to the Chief Executive of Dublin City Council (Mr Owen Keegan) in accordance with Article 15(3) of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003.

Sponsor response

The proposed public notice text that was submitted to the EPA on the 28 June 2018 was sent in parallel to the CEO of St James's Hospital (Mr Lorcan Birthistle) and to the Chief Executive of Dublin City Council (Mr Owen Keegan) and is enclosed with this response. The acknowledgement of receipt (AoR) from Dublin City Council is enclosed.

A copy of the public notice mock-up that was submitted to the EPA on the 4 July 2018 was also sent in parallel to the CEO of St James Hospital and to Dublin City Council. The AoR received on the 3 Sep 2018 from Dublin City Council is enclosed.

Since the sites CEO has not acknowledged receipt of the proposed public notice text or the public notice mock up, these were re-sent to the CEO's office on the 3 Sept 2018 and are enclosed for information. No further acknowledgement has been received from the CEO.

A list of the documents enclosed to support this application is provided in the table below.

Please do not hesitate to contact me should you require further information.

Yours faithfully

[redacted]

List of Documents Enclosed

Document	Filename
Covering letter	1-covering-letter-10sept2018
Dublin Gazette distribution map	2-dublin-gazette-distribution-map-oct2017
St. James Hospital waste management policy	3-sjh-site-waste management-policy-version 6
Disinfectant literature	4-sjh-site disinfectant literature
St James Hospital (SJH) floor plan (GMO storage and administration)	5-sjh crf-floor plan
Dublin city council (DCC) communications relating to the public notice sent and the acknowledgement of receipts	6-dcc-public notice-28 June 2018 6.1-dcc-aor-3 July 2018 6.2-dcc-public notice mock-up-4 July 2018 6.3-dcc-aor -3 Sept 2018
St James Hospital (SJH) CEO communications relating to the public notice sent	7. sjh ceo-public notice-3 Sept 2018 7.1 sjh ceo-public notice -28 June 2018 7.2 sjh ceo-public notice mock-up-3 July 2018

[redacted]

Teresa Roche

From: Bernadette Murray
Sent: 14 September 2018 15:31
To: [redacted]
Cc:
Subject: For the attention of Chief Executive of UniQure Biopharma BVNetherlands
Attachments: RFI2_14092018.pdf

Dear [redacted]

Enclosed please find a request for further information relating to uniQure Biopharma BV's proposed Deliberate Release Clinical Trial notification (B/IE/18/01, G0667-01) submitted to the Irish EPA under the GMO (Deliberate Release) Regulations S.I No 500 of 2003.

Kind regards
Bernie

Bernie Murray
Environmental Protection Agency
P.O. Box 3000
Johnstown Castle Estate
Co Wexford
IRELAND

+353 53 9167252
b.murray@epa.ie

Environmental Protection Agency

Headquarters, PO Box 3000
Johnstown Castle Estate
County Wexford, Ireland
Y35 W821

Ceannchearchrú, Bosca Poist 3000
Eastát Chaisleán Bhaile Sheáin
Contae Loch Garman, Éire
Y35 W821

T: +353 53 9160600
F: +353 53 9160699
E: info@epa.ie
W: www.epa.ie

LoCall: 1890 33 55 99

Chief Executive
Uniqure BioPharma BV
Paasheuvelweg 25A
1105 BP Amsterdam
Netherlands

[redacted]

I would like to draw your attention to a matter arising from our assessment of uniQure Biopharma BV's proposed Deliberate Release Clinical Trial notification (B/IE/18/01, G0667-01) submitted to the EPA under the GMO (Deliberate Release) Regulations S.I. No 500 of 2003, (hereafter referred to as the GMO Regulations).

uniQure, by submitting a notification of intent to make a deliberate release to the EPA is the 'notifier'. The term 'Notifier' is defined under Article 3 of the GMO Regulations as '*any legal or natural person submitting a notification, or where the context so requires, a legal or natural person responsible for a deliberate release or for ... meeting any other requirement of these Regulations in relation to a deliberate release ...*'

You have told us that responsibility for the conduct of the clinical trial in accordance with the trial protocol is to be attributed to the Principal Investigator (PI) (correspondence dated 10/09/2018). The PI was identified as Dr Niamh O'Connell, National Coagulation Centre, St. James' Hospital, Dublin. Neither this person, nor their organisation, St James' Hospital, are party to the notification of intent to make a deliberate release to the Agency.

Article 18(5) of the GMO Regulations states that '*the Agency shall respond in writing to the notifier within 90 days of receipt of the notification by indicating that consent to the deliberate release is either*

(a) granted, with or without conditions, or
(b) refused and the reasons for the refusal.'

Such a consent, if issued, would be issued to the notifier. However, the notifier has no responsibility for overseeing the trial or for implementing the conditions of any consent as may be granted.

Neither the PI nor St. James' Hospital, who have overall responsibility for overseeing the trial and implementing the conditions of a consent, have any liability arising from failure to comply with the conditions of any consent as may be granted.

In the case of a non-compliance, the only recourse the EPA would have is to a consent holder in another member state. This is not satisfactory.
This matter requires resolution before I can proceed to make a recommendation to the Board of the EPA. You are invited to address this anomaly to the EPA's satisfaction.

Please note that Article 8(1) of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003 states *'For the purposes of calculating periods within which the Agency may make a decision under these Regulations, a period of time during which the Agency is awaiting any further information on a notification or an amended notification which it may have requested from the notifier shall not be taken into account.'*.

Therefore the clock shall be stopped until such time as the additional information requested is provided to the Agency.

Sincerely

Bernie .

Bernie Murray
Office of Environmental Sustainability

Teresa Roche

From: [redacted]
Sent: 01 November 2018 15:30
To: Bernadette Murray
Cc: Teresa Roche; Licensing Staff
Subject: G0667-01- AMT-061 GMO DR submission: Response to request for additional information
Attachments: 1. cover letter-rfi response-1nov2018.pdf

Dear Bernie

Please find attached the response to the request for additional information received on the 17 October 2018.

Sincerely

[redacted]

From: Bernadette Murray <B.Murray@epa.ie>
Sent: 17 October 2018 10:42
[redacted]
Cc: Teresa Roche <T.Roche@epa.ie>
Subject: Request for additional information

Dear [redacted]

Further to our telephone conversation yesterday afternoon, enclosed please find a request for further information relating to G0667-01 (B/IE/01/18)
in accordance with Article 19(1) of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003.

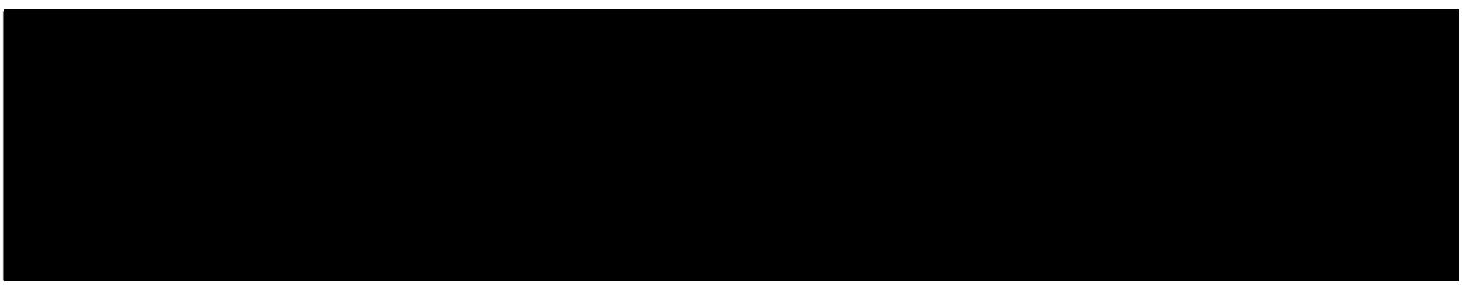
Please note that Article 8(1) of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003 states *' For the purposes of calculating periods within which the Agency may make a decision under these Regulations, a period of time during which the Agency is awaiting any further information on a notification or an amended notification which it may have requested from the notifier shall not be taken into account.'*

Therefore the clock shall be stopped until such time as the additional information requested is provided to the Agency.

Regards
Bernie

Bernie Murray
Environmental Protection Agency
P.O. Box 3000
Johnstown Castle Estate
Co Wexford
IRELAND

+353 53 9167252
b.murray@epa.ie



Environmental Protection Agency
Office of Environmental Sustainability
P.O. Box 3000
Johnstown Castle Estate
Co Wexford
IRELAND

Submission by email to: licensing@epa.ie
cc: b.murray@epa.ie; and T.Roche@epa.ie

1st November 2018

G0667-01, uniQure Biopharma B.V., Deliberate Release Clinical Trial

Response to Request for further information received 7 Oct 2018
(in accordance with Article 19(1) of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003)

Protocol Title:	Phase III, open-label, single-dose, multi-centre multinational trial investigating a serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIXco-Padua, AMT-061) administered to adult subjects with severe or moderately-severe hemophilia B
Protocol ID:	CT-AMT-061-02
IMP:	AAV5-hFIXco-Padua (serotype 5 adeno-associated viral vector containing a codon optimised human factor IX Padua gene)
EPA reference	G0667-01

Dear Dr Murray

Please find below the information requested to progress the GMO submission assessment for the clinical study mentioned above.

Please do not hesitate to contact me should you require further information.

Yours sincerely

[redacted]

[redacted]

1. **EPA request**

Inactivation
Inactivation by incineration is being advocated for all waste types generated. Is there a particular reason why onsite inactivation by autoclaving or disinfection (in the case of liquid waste) cannot take place?

There are no incineration facilities in Ireland, therefore, where will incineration take place?

Sponsor response

The Dublin site employs SCRL (http://www.srcl.com/infectious-waste/) for removal and disposal of their waste (EPA waste license no 54-2). Waste at the site is removed by SRCL in an agreed process to provide a single auditable waste management trail.

SCRL are responsible for incineration of waste and have confirmed that the waste is sent to England for incineration.

Onsite disinfection will occur in areas where material is prepared (pharmaceutical isolator) according to the site's agreed processes.

2. **EPA request**

Monitoring
Section 4.4.5 states that "Observation of patients will be by means of post-administration surveillance for up to 24 hours" and section 4.3 states " ... as blood samples are drawn during the first 3 days after administration of the GMO". If the patient is retained for 24 hours, how is the taking of blood samples during the subsequent 48 hours managed. Please clarify as this aspect is not clear.

Sponsor response
In practice post administration surveillance will be at the clinical study site until approximately 3 hours after the GMO is administered to the patient in order to check for tolerance of the GMO and for potential immediate adverse events; blood samples are taken for C-reactive protein measurement and vector genome detection during this time. Patients may leave the clinical study site after all baseline and post-IMP assessments have been performed and will be provided with an e-diary to enable continuous monitoring between visits. For the management of samples taken between visits, in practice patients will return to the clinic for their scheduled follow up visits (weekly for the first 12 weeks, and monthly from Month 4 to Month 12) which will include providing samples for measurement of efficacy and safety laboratory parameters, hematology and serum chemistry. For any unscheduled sampling/ sampling taken in between scheduled follow-up visits, patients will return to the clinic to have their samples taken; samples will be handled according to the procedures for the scheduled visits.

3. **EPA request**

Monitoring
SNIF, section H5 states
"The body fluids of treated subjects will be monitored until found negative (three consecutive negative samples) for the presence of vector DNA".

[redacted]

Does this relate to all body fluids or just "serum and semen" as suggested under Section H3 of the SNIF?

Why is the presence of vector DNA monitored given that it is non-infectious?

Why isn't the presence of infectious GMO monitored?

Sponsor response
Body fluids relates to serum and semen as listed in Section H3 of the SNIF.

In non-clinical and clinical studies, it is generally acceptable for shedding samples to be assessed for the presence of vector-derived DNA, and not for the presence of infectious particles. This is because quantitation of infectious AAV particles in biological matrices requires complex bioassays. In contrast, quantitation of vector-derived DNA using polymerase chain reaction- (PCR-) based methods is relatively simple, robust and precise. A detected copy of vector DNA does not necessarily represent an infectious vector particle, but might also represent DNA from a degraded vector particle, a particle that has been taken up by a cell, or a cell which has been transduced by the vector (e.g. leukocytes or epithelial cells of the bladder). In preclinical studies on recombinant AAV it has been shown that urine containing AAV vector DNA does not contain infectious particles (Favre *et al.*, 2001), and that infectious vector is restricted to the plasma compartment and cleared from the circulation within 48 to 72 hours after infusion.

One group with extensive experience in the quantitation of infectious particles (Salvetti *et al.*, 2008) performed a non-clinical study in which shedding samples were analysed for the presence of vector-derived DNA by PCR, as well as for infectious vector particles by bioassay (Favre *et al.*, 2001). In this study, cynomolgus monkeys were dosed intramuscularly with an AAV2-based vector. At various time points after infusion, bodily fluids and excretions were collected and analysed. Serum, urine, faeces, saliva, and lachrymal and nasal fluids were all PCR-positive until 7 days after vector infusion. In contrast, after rAAV administration "rAAV infectious particles were unambiguously detected only in the serum of all the animals" and "infectious particles were never detected in the serum of any animal past the first week". The methods used to assess vector DNA and infectious particles displayed similar sensitivity, hence the results demonstrated that the vector DNA in the shedding samples did not represent infectious vector particles, but rather degraded vector particles or remnants of transduced cells.

It is not known whether recombinant AAV shed in semen is infectious or, like AAV shed in the other fluids, represents non-infectious vector DNA. In either case, the likelihood of horizontal or vertical transmission cannot be excluded. Consequently the use of a condom during the trial in the period from administration of the AAV5-hFIX until the AAV5 vector has been cleared from semen is required.

Based on the described shedding through serum and based on the unknown shedding through semen these two compartments have been included in shedding analysis in the context of the AMT-061 clinical trial as evidenced by negative analysis results for AAV5 vector for at least three consecutively collected semen samples. As soon as three consecutive samples have been tested negative through QPCR testing patients will be relieved from the required use of contraceptives.

References

Favre *et al.* (2001) Molecular Therapy. 4:559-566

Salvetti *et al.* (2008) Human Gene Therapy. 9:695-706

[redacted]