Bernadette Murray

From: Bernadette Murray
Sent: 16 May 2019 15:52
To: [redacted]
Cc: Teresa Roche; Licensing Staff; [redacted]
Subject: RE: G0667-01, uniQure Biopharma B.V., Deliberate Release Clinical Trial-Response to consent conditions-Clarifications-EPA-Ireland

Tracking:

Recipient	Delivery
[redacted]	
Teresa Roche	Delivered: 16/05/2019 15:52
Licensing Staff	Delivered: 16/05/2019 15:52
[redacted]	

Dear [redacted]

Thank you for the information received which is satisfactory.

Kind Regards
Bernie

Bernie Murray
EPA
00353 53 9167252
b.murray@epa.ie

From: [redacted]
Sent: 13 May 2019 12:21
To: Bernadette Murray <B.Murray@epa.ie>
Cc: Teresa Roche <T.Roche@epa.ie>; Licensing Staff <licensing@epa.ie>; [redacted]
Subject: G0667-01, uniQure Biopharma B.V., Deliberate Release Clinical Trial-Response to consent conditions-Clarifications-EPA-Ireland
Importance: High

Dear Bernie

Please see attached the clarifications related to the response to the consent conditions submitted on the 26 April 2019 and your request for clarification on the 2 May 2019.

Please let me know if the information is satisfactory and if further information is required.

Kind regards
[redacted]

From: Bernadette Murray <B.Murray@epa.ie>
Sent: 02 May 2019 09:22
To: [redacted]

Subject: RE: G0667-01, uniQure Biopharma B.V., Deliberate Release Clinical Trial-Response to consent conditions-EPA-Ireland

Dea [redacted]

Further to our telephone conversation yesterday I have a few other points I would like clarification on.

On page 3 of 5 of the response under section 2c procedure 005 refers to "Preparation of AT-409" what does this relate to? Should this be AMT-061?

Also of the SOPs listed, which relate to training as stipulated under the consent or how is training dealt with?

Many thanks
Bernie

Bernie Murray
EPA
00353 53 9167252
b.murray@epa.ie

From: [redacted]
Sent: 26 April 2019 10:28
To: Teresa Roche <T.Roche@epa.ie>; Bernadette Murray <B.Murray@epa.ie>
Cc: Licensing Staff <licensing@epa.ie>; [redacted]
Subject: G0667-01, uniQure Biopharma B.V., Deliberate Release Clinical Trial-Response to consent conditions-EPA-Ireland
Importance: High

Dear Bernie

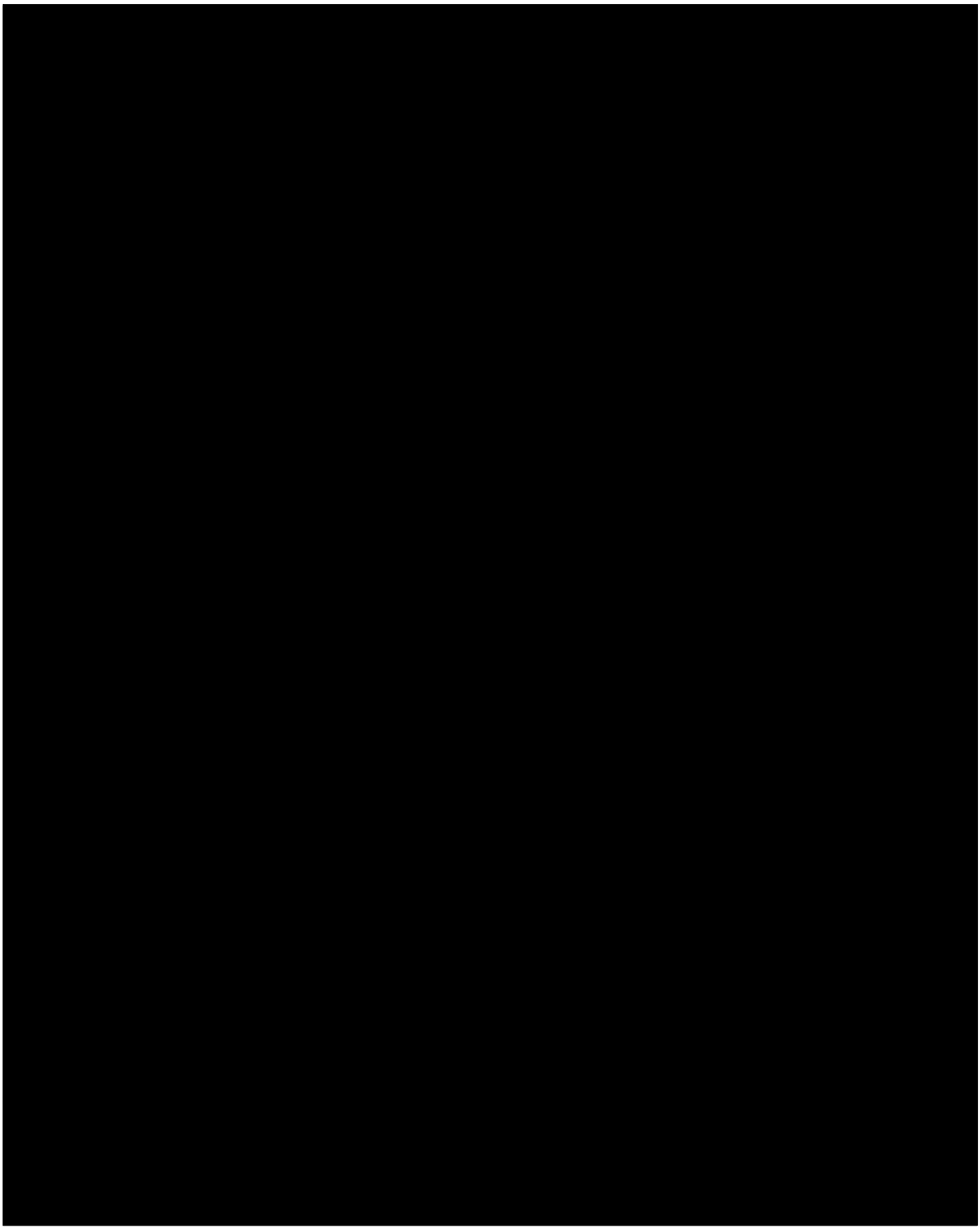
Please find attached the response to the consent conditions received on the 21 November 2018 (EPA reference G0667-01).

Please note: The date of trial commencement, when the IMP will be shipped to the site, is not known at the present time. The actual date for IMP shipment will be provided to the EPA in around 6-months' time when all baseline assessments have been performed and patient eligibility is confirmed; the information will be provided 2 weeks before the IMP is shipped to the site.

Please do not hesitate to contact me should further information be required.

Sincerely

[redacted]



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

14 May 2019

Further Clarifications
(Response to Consent Conditions submitted 26 April 2019)

G0667-01, uniQure Biopharma B.V., Deliberate Release Clinical Trial
(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 clarifications related to the response to questions date 26 April 2019.

Please note the change in pharmacist for the Dublin site has changed and is addressed in the clarifications below.

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

Yours sincerely,

[redacted]

Clarifications related to Question 2

2. EPA request

To be provided prior to trial commencement

a. The agreement put in place with St James's Hospital describing the delegation of responsibility, (Condition 4. 7) should be between the notifier (uniQure) and the site.

b. The notifier shall provide the name and contact details of the PI and the Pharmacist (i.e. telephone number, and email address) (Condition 4.5)

c. The notifier shall implement SOPs set out under Condition 6.7.1: On page 3 of 5 of the response under section 2c procedure 005 refers to "Preparation of AT-409" what does this relate to? Should this be AMT-061?

Of the SOPs listed, which relate to training as stipulated under the consent or how is training dealt with?

Sponsor response

a. The agreement was provided on 26 April 2019. A letter is enclosed in Appendix 1 to confirm the PI and St. James's Hospital (CFR) itself have entered into a clinical trial agreement with the notifier uniQure biopharma BV, concerning the aforementioned Phase III trial. uniQure biopharma B.V. acknowledges, that the conditions set out in the Agreement Letter provided on the 26 April 2019 meets the terms and conditions as agreed upon in the clinical trial agreement with the PI (Dr Niamh O'Connell) and the clinical site (St. James's Hospital).

b. The name and contact details of the PI was provided on 26 April 2019. The Pharmacist information has changed and is provided below

Pharmacist

[redacted]

c. Regarding SOP "SSP CRFSJ 0177 SSP 005 Preparation of AT-409", was incorrect. The correct SOP is "SSP CRFSJ 0177 SSP 004 Preparation of AMT-061 Infusion" (please see Appendix II for the SOP).

Regarding the SOPs listed in the response provided on the 26 April 2019 and how the training is dealt with, this function would fall within the operational structure of the clinical study site – i.e. there is an SOP for training and management of training records. The SOPs related to the tasks listed would have a training record sheet, attached to the SOP, which would be signed by staff to confirm they have been trained.

[redacted]

Appendix I – Agreement Clarification

[redacted]

uniQure

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

Amsterdam, 06 May 2019

G0667-0I, uniQure biopharma B.V., Deliberate Release Clinical Trial

Protocol Title: Phase III, open-label, single-dose, multi-centre multinational trial investigating a serotype 5 adena-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AA V5-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 adena-associated viral vector containing a codon optimised human factor IX Padua gene)

EPA reference: G0667 -0 I

Dear Madam / Sir,

Regarding the agreement sent to the EPA on the 26 April 2019, relating to the response to the consent conditions Request 2a, I hereby confirm on behalf of the notifier uniQure biopharma B.V. (also the Sponsor of the Clinical Trial), that:

The PI and St. James's Hospital (CFR) itself have entered into a clinical trial agreement with the notifier uniQure biopharma BV, concerning the aforementioned Phase III trial. The Sponsor acknowledges, that the conditions set out in the Agreement Letter provided on the 26 April 2019 meets the terms and conditions as agreed upon in the clinical trial agreement with the PI ([redacted] and the clinical site (St. James's Hospital).

Should you have any questions please do not hesitate to contact me.

Yours faithfully,

[redacted]

Appendix II - SSP CRFSJ 0177 SSP 004 Preparation of AMT-061 Infusion

[redacted]

Study Specific Procedure

CRFSJ 0177-SSP-004

Wellcome - HRB Clinical Research Facility at St. James's Hospital

Study Title	CT-AMT-061-02: Phase III trial of AMT-061 in subjects with severe or moderately severe haemophilia B
Study Number	CRFSJ 0177
Principal Investigator	[redacted]
SSP Title	**Preparation of AMT-061 Infusion**

Document No:	Version No:	Effective Date:	Supersedes Version:
CRFSJ 0177-SSP-004	1	30th April 2019	N/A

Prepared by:

Signature: [redacted] Date: 17 Apr 2019

Print Name:

Title: Chief II Pharmacist CRF

Reviewed by:

Signature: [redacted] Date: 17April2019

Print Name:

Title: Senior Research Pharmacist CRF

Approved by:

Signature: [redacted] Date: 18/Apr/2019

Print Name:

Title: Principal Investigator

Study Specific Procedure **CRFSJ 0177**		Wellcome - HRB Clinical Research Facility at St. James's Hospital
Title: **Preparation of AMT-061 Infusion**		
Document No: CRFSJ 0177-SSP 004	Version No: 1	Effective Date:

TABLE OF CONTENTS

Study Specific Procedure CRFSJ 0177		Wellcome - HRB Clinical Research Facility at St. James's Hospital
Title: **Preparation of AMT-061 Infusion**		
Document No: CRFSJ 0177-SSP 004	Version No: 1	Effective Date:

1. Purpose

The purpose of this Study Specific Procedure (SSP) is to describe the step-by-step procedure for the preparation of the Genetically Modified Organism (GMO) Investigational Medicinal Product (IMP), AMT-061 Infusion for the CT-AMT-061-02 trial.

2. Scope

- This applies to aseptic preparation of the AMT-061 infusion for the CT-AMT-061-02 trial in the Wellcome-HRB Clinical Research Facility at St James's Hospital (CRF). Preparation will occur in the ATIMP Isolator in the CRF ATIMP Clean Room (CRF28D).
- This applies to staff involved in preparing the infusion, i.e. trained and delegated study team members.

3. Responsibilities

a) The Principal Investigator (PI) is responsible for all activities related to this trial undertaken at the CRF.

b) The Chief II Pharmacist (CRF) is responsible for training staff in this SSP and ensuring the activities described are carried out appropriately.

c) Only staff trained in this SSP and in using the CRF ATIMP Clean Room Isolator should be involved in preparation of the AMT-061 infusion.

4. Related Documents

a) IMP Handling Manual CT-AMT-061-02 Version 2, 06Dec2018

b) CRF.PHR.018 Cleaning the ATIMP Clean Room

c) CRF.PHR.019 Cleaning the ATIMP Clean Room Isolator

d) CRF.PHR.020 Operation of the ATIMP Clean Room

e) CRF.PHR.021 Operation of the ATIMP Clean Room Isolator

f) CRFSJ 0177 – SSP 002 PPE for GMO IMP Handling

g) CRFSJ 0177 – SSP -001 GMO IMP Access, Storage and Transport

h) CRFSJ 0177 – SSP 005 Management of GMO Waste

i) AMT-061 Preparation Worksheet

j) AMT-061 Patient Pack Accountability Log

k) Traceability Record for diluted AMT-061 Infusion Bag

5. Abbreviations

Abbreviation	Term
ATIMP	Advanced Therapy Investigational Medicinal Product

CRA	Clinical Research Associate
CRF	Wellcome-HRB Clinical Research Facility at St James's Hospital
CTM	Clinical Trial Manager
EPA	Environmental Protection Agency
GMO	Genetically Modified Organism
HRB	Health Research Board
IMP	Investigational Medicinal Product
PI	Principal Investigator
PPE	Personal Protective Equipment
SJH	St James's Hospital

6. Procedure – Preparation of AMT-061 Infusion

Activities Prior to Dose Preparation

6.1 Day before Dosing (12-24 hours before dosing)

6.1.2. On the afternoon before the planned dosing day, remove the AMT-061 Patient Pack from the freezer for thawing (for a **minimum of 12 hours and a maximum of 24 hours**) using appropriate personal protective equipment (PPE). For appropriate PPE, refer to *CRFSJ 0177 – SSP 002 PPE for GMO IMP Handling*.

6.1.3. Place the patient pack in a leak-proof bag in a designated and labelled blue tray at room temperature in the CRF Pharmacy on a separate workbench to where other dispensing activity may occur. The AMT-061 vials are provided in a customized secondary packaging box which should ensure they are protected from light during thawing.

6.1.4. Complete the AMT-061 Preparation Worksheet sections on:

- Patient information
- Calculations
- Vial lot numbers
- Date and time of removal of vials from freezer

6.1.5. Leave the worksheet next to the blue tray to be completed the following day during preparation.

6.2. Dosing Day

6.2.1. All activities for preparation of the AMT-061 infusion on dosing day will occur in the CRF ATIMP Clean Room. Preparation of the AMT-061 infusion should only be performed by a trained and delegated pharmacist. A second trained and delegated member of the study team will need to be present to provide a volume and preparation check.

6.2.2. No other products may be prepared in the ATIMP Clean Room while the AMT-061 is being prepared.

6.2.3. A full cleaning of the ATIMP Clean Room and the ATIMP Clean Room Isolator should be performed prior to the start of preparation (as per CRF.PHR.018 and CRF.PHR.019).

6.2.4. There should be at least 1 hour between the start of cleaning and the start of preparation in which the Clean Room cannot be used to prepare any other medications.

6.2.5. Prepare and print four (4) prepack labels for: the infusion bag, the light protection cover bag, the AMT-061 Preparation Worksheet and the CRF pharmacy activity record book. The label should include the following information:

- Product name: Diluted AMT-061
- Protocol number: CT-AMT-061-02
- Patient MRN: XX-XX-XXX
- Patient Name
- Patient Trial Identification Number
- Calculated dose for patient (calculated as 2×10^{13} gc/kg)
- Appropriate expiration date & time: 24 hours after first AMT-061 vial break
- Storage condition: Controlled Room Temperature and protected from light
- Cautionary statement "Contains Genetically Modified Organisms"

6.2.6. Once prepared the infusion bag should be protected from light during storage and transport. Prepare a light protection cover bag by attaching the prepack label (as per 6.2.5) prior to preparing the infusion bag.

6.2.7. Ensure the following supplies are available before preparation:

a) Sodium Chloride (NaCl) 0.9% Infusion Bag 500mL
b) Equashield® Vial Adaptor (1 vial adaptor required per vial)
c) Infusion giving set
d) Equashield® 20mL syringe units
e) Equashield® Spike Adaptors
f) Equashield® Spike Adaptor-W
g) Alcohol Prep Pads
h) Spill Kit

Patient Dose Preparation

6.3. Preparing for Infusion

6.3.1. Appropriate PPE should be worn when undertaking preparation activities (refer to *CRFSJ 0177-SSP 002 PPE for GMO IMP Handling*).

6.3.2. The thawed AMT-061 Patient Pack will be transported in a leak-proof bag in a designated and labelled blue tray from the CRF Pharmacy (CRF28A) to the CRF

ATIMP Clean Room (CRF28DD) for preparation. Refer to *CRFSJ 0177 – SSP- 001 GMO IMP Access, Storage and Transport.*

6.3.3. Transfer all required materials as per 6.2.7 (a)-(g) and the thawed AMT-061 Patient Pack into the ATIMP Clean Room Isolator as per CRF.PHR.021 (Operation of ATIMP Clean Room Isolator).

6.3.4. A second trained and delegated member of the study team who is performing the volume and preparation check will record the required information on the AMT-061 Patient Pack Accountability Log and the AMT-061 Preparation Worksheet during preparation.

6.3.5. Clean the rubber port of the 500mL sodium chloride (NaCl) 0.9% infusion bag with a sterile Alcohol Pad and allow to air dry.

6.3.6. Attach the Spike Adaptor-W to the infusion bag. Using Equashield® 20mL syringe units withdraw a volume of 0.9% NaCl from the infusion bag that is equal to the volume of AMT-061 to be added. The volume of 0.9% NaCl to be removed will vary based on the patient weight. Discard this syringe into a sharps bin.

6.3.7. Remove the Spike Adaptor-W for the infusion bag and clean the rubber port again with an Alcohol Prep Pad and allow to air dry.

6.3.8. Attach the Spike Adaptor to the infusion bag.

6.3.9. Visual Inspection: Inspect each vial from the AMT-061 Patient Pack for complete thawing, particulate matter, and discolouration. Do not excessively shake the vials during this inspection.

6.3.9.1. If thawing is incomplete, leave the vials in the isolator to thaw further but ensure dilution of AMT-061 occurs within 24 hours after removing from the freezer.

6.3.9.2. If foreign particles are observed or if the solution is discoloured, do not use the vial and immediately contact the Clinical Research Associate (CRA) and the uniQure Clinical Trial Manager (CTM).

6.3.9.3. The second member of the study team should document the results of this visual inspection on the AMT-061 Patient Pack Accountability Log.

6.3.10. Gently swirl each vial 3 times for 10 seconds to homogenize the AMT-061 solution.

6.4. Preparation of the Infusion

6.4.1. Remove the plastic flip-off cap from the vials and disinfect the rubber stopper with an Alcohol Prep Pad and allow to air dry.

6.4.2. Attach an Equashield® Vial Adaptor to each vial. Person performing volume and preparation check should record the time when a vial adaptor is attached to the first vial ('time of first vial break') on the AMT-061 Preparation Worksheet.

6.4.3. Withdraw the AMT-061 solution from a vial using an Equashield® 20mL syringe unit. Note: Each vial contains approximately 10mL of AMT-061 solution. Avoid foaming throughout the process.

6.4.4. Slowly inject the AMT-061 solution from the syringe(s) into the infusion bag through the spike adaptor. Do not add the AMT- 061 solution into the airspace contained within the infusion bag.

6.4.5. Repeat steps 6.4.3 and 6.4.4 with additional syringes up to the total calculated volume required for the patient dose. Once 9 syringes have been connected to the spike adaptor on the infusion bag, the spike adaptor should be replaced with a new one.

6.4.6. Gently invert the infusion bag 3 times to mix the solution. Avoid shaking or excessive agitation.

6.4.7. Connect the infusion line to the 500mL bag of diluted AMT-061 and prime the line with 0.9% NaCl. Note: This step must be performed just before transport of the prepared infusion bag to the CRF Isolation Room for administration to the patient.

6.4.8. Remove the 500mL bag of diluted AMT-061 and prepared infusion line from the isolator. Transfer any waste materials out of the isolator too. For disposal of waste materials, refer to *CRFSJ 0177-SSP 005 Management of GMO waste*.

6.4.9. Review the AMT-061 Patient Pack Accountability Log, the AMT-061 Preparation Worksheet and the prepack labels with the second member of the study team to ensure all required information is recorded and then both members of the study team should sign the AMT-061 Preparation Worksheet.

6.4.10. Complete the required information on the Traceability Record for diluted AMT-061 Infusion Bag.

6.4.11. Attach the prepared prepack label to the infusion bag and cover the bag with the light protection cover prepared in 6.1.9 above.

6.5. Transfer to Administration Room

6.5.1. Transport the infusion bag and infusion line in a leak-proof bag in a designated blue tray labelled with the text "Contains Genetically Modified Organisms" to the CRF Isolation Room (CRF28C) for immediate administration to the patient. Avoid any shaking or excessive agitation during transport.

6.5.2. The Traceability Record for diluted AMT-061 Infusion Bag should also be transported to the CRF Isolation Room and the remaining sections of the record should be completed during and after administration.

7. Revision History

New document

Teresa Roche

From: [redacted]
Sent: 26 April 2019 10:28
To: Teresa Roche; Bernadette Murray
Cc: Licensing Staff; [redacted]
Subject: G0667-01, uniQure Biopharma B.V., Deliberate Release Clinical Trial-Response to consent conditions-EPA-Ireland
Attachments: AMT-061-response to consent conditions-26apr2019-IE.pdf

Importance: High

Dear Bernie

Please find attached the response to the consent conditions received on the 21 November 2018 (EPA reference G0667-01).

Please note: The date of trial commencement, when the IMP will be shipped to the site, is not known at the present time. The actual date for IMP shipment will be provided to the EPA in around 6-months' time when all baseline assessments have been performed and patient eligibility is confirmed; the information will be provided 2 weeks before the IMP is shipped to the site.

Please do not hesitate to contact me should further information be required.

Sincerely

[redacted]

[redacted]

Privacy Statement: Our Privacy Statement explains what we do with your personal data, whether you are visiting our website, corresponding with us or using our services. It describes how we collect, use and process your personal data, and how, in doing so, we comply with our legal obligations to you.

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

26 April 2019

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

Response to Consent Conditions received 21 Nov 2018
Information to be submitted to the EPA prior to trial commencement

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 to be submitted to the EPA prior to trial commencement as per the Consent Conditions for the clinical study mentioned above.

Please note in the response to questions (#1), regarding incineration of waste by SCRL, SCRL have confirmed that the waste is sent to Belgium instead of England for incineration (please refer to response letter dated 1 November 2018).

In compliance with the General Data Protection Regulation (EU) 2016/679 please can you keep all personal information in this response confidential.

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

Yours sincerely,

[redacted]

1. **EPA request**

To be provided 2 weeks prior to trial commencement

a. 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.

b. The notifier shall also provide the date of trial commencement.

Sponsor response

a. The details of the person in the employ of uniQure Biopharma BV with responsibility for overseeing the performance of this clinical trial at St James's Hospital is:

Senior Clinical Trial Manager

[redacted]

b. The date of trial commencement when the IMP will be shipped to the site is not known at the present time. The product will be supplied to the site once the suitability of the patient has been confirmed during the initial screening stage, which is expected to be in around 6 months. IMP will therefore only be shipped to the site for patient administration once all baseline assessments have been performed and eligibility is confirmed. The actual date for IMP shipment will be provided to the EPA in around 6-months' time; the information will be provided 2 weeks before the IMP is shipped to the site.

2. **EPA request**

To be provided prior to trial commencement

a. A copy of the agreement put in place with St James's Hospital describing the delegation of responsibility, (Condition 4. 7)

b. The notifier shall provide the name and contact details of the PI and the Pharmacist (i.e. telephone number, and email address) (Condition 4.5)

c. The notifier shall implement SOPs set out under Condition 6.7.1

d. The notifier shall inform the EPA of the position of the person responsible for reports/ records (Condition 9.4)

[redacted]

Sponsor response

a. A copy of the agreement put in place with St James's Hospital is enclosed with this response (please see Appendix 1).

b. The name and contact details of the PI and the Pharmacist are below:

Principle Investigator

[redacted]

Pharmacist

[redacted]

c. The following procedures that will be implemented for AMT-061 are in place and fulfil Condition 6.7.1:

SSP CRFSJ 0177 SSP 001 GMO IMP Access, Storage, and Transport
SSP CRFSJ 0177 SSP 002 PPE for GMO Procedures
SSP CRFSJ 0177 SSP 003 Receipt of IMP
SSP CRFSJ 0177 SSP 004 Management of GMO Waste
SSP CRFSJ 0177 SSP 005 Preparation of AT-409
SSP CRFSJ 0177 SSP 006 Procedure for GMO spills
SOP CRF.PHR.006 Temperature Monitoring in the CRF Pharmacy
SOP CRF.PHR.0XX Cleaning of Gene Therapy Clean Room suite
SOP CRF.PHR.0XX Cleaning of Gene Therapy Clean Room Isolator

d. The position of the person responsible for reports/ records is shown below:

[redacted]

[redacted]

3. EPA request

To be available on request

a. SOPs set out under Condition 6.7.1

b. List of all positions, persons and their deputies responsible for the conduct of the clinical trial (Condition 7.1)

c. GMM Waste inactivation records

Sponsor response

a. The SOPs under Condition 6.7.1 are available on request.

b. A list of persons responsible for the conduct of the clinical study is available on request.

c. GMM waste inactivation records is available on request.

[redacted]

Appendix 1 – Agreement

[redacted]

Wellcome - HRB
Clinical Research Facility
at St. James's Hospital

St. James's Hospital
Dublin 8
Ireland

Tel: +353 (0)1 410 3900
Email crfsjh@tcd.ie
Web: www.sjhcrf.ie

Clinical Director: Professor Martina Hennessy MB BCh BAO FRCP PhD
Associate Director: Dr David Kevans MB BCh BAO MRCPI MD

[redacted]
Consultant Haematologist,
National Coagulation Centre,
St. James's Hospital,
St James's Street,
Dublin D08 A978

9th April, 2019

Re: CRFSJ 0177 - Phase III, open-label, single-dose, multi-center 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 haemophilia B. CT-AMT-061-02. EudraCT Number 2017-004305-40

Dea[redacted]

In response to your application dated 02-APR-2018 to the Wellcome - HRB Clinical Research Facility at St James's Hospital (CRF), which was reviewed 19-SEP-2018, I am pleased to inform you that your request has been approved subject to the conditions set out in this Agreement Letter. The CRF will assist with the scope of activities outlined in Annex 1. This Agreement Letter outlines the roles and responsibilities of both the Principal Investigator (PI) being supported by the CRF and the CRF and its staff.

Role and Responsibilities of the Principal Investigator (PI)
The PI is accountable and responsible for the conduct of the Trial at Clinical Research Facility, St James Hospital. The PI should be confident in providing assurance to regulators, research subjects and the CRF that the:

- Rights, safety and well-being of trial subjects are protected
- Data is accurate and of a consistent high quality
- Reported results are credible and verifiable.

The support the CRF provides to the Trial does not diminish the PI's responsibilities. The PI must work in collaboration with the CRF to ensure compliance with ICH GCP guidance[1] and applicable legislation; therefore, the PI is responsible for the following:

1. Conducting the Trial in compliance with the approved protocol (including any approved amendments).

[1] GCP is an international ethical and scientific quality standard for designing, conducting and recording and reporting trials/research that involve the participation of human subjects. (See http //ich.org/)

2. Ensuring that only eligible subjects are recruited into the Trial.
3. Ensuring all necessary approvals, including independent Research Ethics Committee (REC) approval, local hospital approval and, if applicable, Health Products Regulatory Authority (HPRA) approval, are in place prior to commencement of the Trial.
4. Obtaining approvals for any subsequent protocol amendments following commencement of the Trial.
5. Ensuring that each individual involved in conducting the Trial is qualified by education, training and experience and complies with the requirements set down in ICH GCP guidance.
6. Ensuring all staff are trained and appropriate delegation of trial duties is in place and documented prior to staff carrying out duties. Training records must be maintained, including records of ICH GCP training.
7. Ensuring that on-going training is carried out as required, including training in any protocol amendments.
8. Ensuring that the Trial and the site are prepared at all times for an audit or inspection. The PI must inform the CRF immediately if notified of an impending audit or inspection. Any results or reports from these audits will be made available to the CRF. In the event of a sponsor audit, the CRF requires a notification period of at least one month.
9. Notifying CRF staff of any equipment they intend to bring into the CRF for use in the Trial. The PI is responsible for any equipment they bring into the CRF. All equipment should be fit for purpose and serviced and calibrated appropriately. The PI is responsible for maintaining service/ calibration records and providing these for inspection on request.
10. Ensuring adequate medical care is provided to subjects attending the CRF and for any continuing care required as a result of an adverse event.
11. Overseeing all Serious Adverse Events (SAE) and reporting these to the Trial sponsor immediately (within 24 hours) and following up within the correct time frame.
12. In the event that breaches of GCP are identified, the PI is responsible for ensuring that appropriate remedial action is taken and all issues are documented.
13. Notifying the CRF in the event of the Trial being put on hold or terminated early. All participants must be notified, and the Accrued costs will be paid in accordance to the study protocol.
14. Archiving of all data in relation to the Trial and abiding by the Data Protection Acts 1988 and 2003. Documentation should be retained for a minimum period of 5 years, unless otherwise directed by the Trial sponsor or funding body. For data used to support a marketing authorisation, documentation must be retained for at least 15 years after completion of the Trial or at least two years after the granting of the last marketing authorisation.

Role and Responsibilities of the Clinical Research Facility

The CRF will provide experienced research staff, equipment and facilities maintained to the standards of ICH GCP to the Trial as detailed in Annex 1. The CRF has procedures in place to care for participants who require emergency care during their visit to the CRF, and if required will assist patient transfer to the Emergency Department of St James's Hospital.

While it is recognised that CRF staff will become a key part of the PI's research team, CRF staff allocated to studies are employees of the CRF and will be ultimately accountable to the Directors of the facility.

Additional Conditions of Approval

The progress of the Trial in the CRF will be reviewed after the first 6 months and then at agreed intervals thereafter.

The PI must agree to duly acknowledge the CRF and its funders in publications, presentations, and posters with the following statement:

"We would like to acknowledge the assistance and support of the Wellcome - HRB Clinical Research Facility at St. James's Hospital in providing a dedicated environment for the conduct of high quality clinical research activities"

As part of quality assurance, the CRF employs an internal audit procedure to ensure continuous improvement of the quality systems. The PI and their team are expected to cooperate with the CRF in the event of the Trial forming part of an audit.

The CRF welcomes regular feedback and engagement from the PI and their team. The PI is encouraged to highlight any concerns about the level and/or quality of support provided by the CRF to the Director or Associate Director of the CRF. All necessary action will be taken to ensure continuation of a high quality and robust service.

Please signify your agreement by signing Annex 2 and return the signed Agreement Letter to the CRF's Assistant Director of Nursing (ADON).

Yours sincerely,

Professor Martina Hennessy
Director

CC Derval Reidy, Assistant Director of Nursing (ADON)

Annex 1: **Conditions of Approval**

1. **Scope of Support**

<table>
<tr><td>Site:</td><td>Clinical Research Facility, St James Hospital</td></tr>
<tr><td>Timetable of support:</td><td>Potential Participants will be identified from the Principal Investigator's (PI) (or delegate) own cohort of patients at the pre-screening stage. The PI (or delegate) will also be responsible for protocol related events as per delegation log. There will be a total of 38 study visits: All visits will take place in the CRF
Mondays or Tuesdays have been identified as the main day for study related activity. A total of 2 to 5 patients will be recruited into this study. The CRF will provide a clinic room, a Research Nurse, Pharmacy services, blood draws, data coordination and management; pharmacy services as per delegation log. All pharmacy, consultant and nursing staff will be suitably trained in the handling and manipulation of GMO.</td></tr>
<tr><td>Rooms and equipment to be provided:</td><td>Rooms will be booked at least one week in advance on a named patient basis by the NCC Study Coordinator or the CRF Research Nurse. Rooms will be booked if available.
<table><tr><td>Date</td><td>Time</td><td>Duration</td><td>CRFSJH Study no</td><td>Patient Study No</td><td>MRN</td><td>DOB</td><td>Initials</td></tr></table>
Calibrated and certified weight/height scales, vital sign monitors and ECG machine will be provided by the CRF.
All trial related equipment and consumables will be provided by the Sponsor .The NCC will provide phlebotomy consumables.
CRF Gene Therapy Clean Room suite will be available as required for trial activities.</td></tr>
<tr><td>Medical Cover:</td><td>Must be provided by the Principal Investigator (PI). A trial Doctor listed on the delegation log must be on-campus at each and every participant visit</td></tr>
<tr><td>Nursing Activity:</td><td>The CRF Research Nurse will be responsible for and aid the NCC Study Coordinator with nursing activity as per delegation log for recruited participants into the study. This includes – vital signs, phlebotomy, and IMP infusion, AE/SAE reporting for protocol prescribed visits, data entry and management including regular review of data queries. SAE management and out of hours cover will be covered by the NCC and/or PI. The CRF Nurse will assist as required in reporting SAEs. The CRF Research Nurse is not responsible for pre-screening or recruiting participants into the study.
As per study protocol the CRF research nurse will be responsible for monitoring of body fluids such as blood and semen as per protocol. Vector genome detection (through semen samples) is conducted as per protocol until 3 consecutive negative samples are obtained.</td></tr>
</table>

Pharmacy Activity:	The CRF Pharmacy will be delegated responsibility for reception, storage and preparation of the GMO as per protocol and CRF gene therapy SSPs. The CRF Pharmacy will be responsible for reception, storage, preparation and administration of the GMO as well as the disposal and treatment of all GMO contaminated materials used during the course of the clinical trial.
Participant types covered by the Trial/Study:	Male subjects aged ≥18 years with congenital hemophilia B with known severe or moderately severe FIX deficiency (≤2% of normal circulating FIX) for which the subject is on continuous routine Factor IX prophylaxis
Limits to data and samples collected:	As per protocol. Not to exceed scope permitted by REC approval
Sample processing responsibilities:	CRF will facilitate collection of samples. However, sample processing will be the responsibility of the investigators and the SJH Clinical Centre for pathology and laboratory medicine.
eCRF Development and Support:	The eCRF development and support will be the responsibility of the Sponsor
Data Management and data capturing:	Both the CRF and NCC Study Coordinator will upload the data onto the eCRF. Data management will ultimately, be the responsibility of the Principal Investigator. SAE reporting and management will be primary the responsibility of the NCC coordinator, with back up cover from the CRF research nurse in the event of planned or unplanned leave. The NCC Study coordinator will be responsible for managing the monitoring visits A copy of each monitoring report must be provided to the CRF. The CRF must be notified once known of an inspection or audit to the study.
Training	The CRF will ensure only trained and delegated staff will perform activities related to this trial. The CRF will maintain training logs and comply with trial delegation logs.
Waste Management	The CRF will ensure the correct disposal and treatment of all GMO contaminated materials used during the course of the clinical trial.
Other Activities:	CRF resources dedicated to this trial are not to be diverted to other research studies not covered by the scope of their application and associated approval.

2. <u>The PI must provide the following documents to the ADON:</u>

[Select and amend as necessary all that apply – delete this instruction prior to issue]

<u>Document</u>
Copy of all documents submitted to the Research Ethics Committee (REC) seeking their approval for the Trial
Copy of REC approval letter

Annex 2: Principal Investigator Agreement

Acknowledgement by Principal Investigator:

I the undersigned have read and understood this Agreement Letter and agree that the support offered is conditional on compliance with conditions specified above.

[redacted]

Date: 15 APR 2019

[PI Print Name]

Acknowledgement by person nominated for On-Site Medical Cover while patients are in the CRF.

I, the undersigned, am aware of, and understand, my responsibilities with respect to providing on-site medical cover for participants of this trial/study.

[redacted]

[redacted]

Date: 15 APR 2019

Note: The CRF must be notified of any changes to the person nominated for on-site medical cover