PART 1 (COUNCIL DECISION 2002/813/EC)

SUMMARY NOTIFICATION INFORMATION FORMAT FOR THE RELEASE OF GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS IN ACCORDANCE WITH ARTICLE 11 OF DIRECTIVE 2001/18/EC

In order to tick one or several possibilities, please use crosses (meaning x or X) into the space provided as (.)

A. General information

1. 1] Details of notification

(a) Member State of notification: The Netherlands

(b) Notification number: B/NL/14/008

(c) Date of acknowledgement of notification: 17/12/2014

(d) Title of the project

An open-label, uncontrolled, single-dose, dose-escalation, multi-centre trial investigating the safety and efficacy of systemic administration of AAV5-hFIX, an adeno-associated viral vector containing a codon-optimised human factor IX gene, to severe haemophilia B

(e) Proposed period of release: From Q3-2014 until Q4-2015

2. 2] Notifier

Name of institution or company:
uniQure Biopharma B.V.
Meibergdreef 61
1105 BA Amsterdam
The Netherlands

3. 3] GMO characterisation

(a) (a) Indicate whether the GMO is a:

viroid	(.)
RNA virus	(.)
DNA virus	(X)
bacterium	(.)
fungus	(.)
animal	
- mammals	(.)
- insect	(.)
- fish	(.)

- other animal (.) specify phylum, class …

(b) (b) Identity of the GMO (genus and species)
Parvoviridae
Genus: Dependovirus
Species: AAV-derived replication-deficient viral vector
The complete name of the vector is: Recombinant adeno-associated viral vector containing the codon-optimized human coagulation factor IX cDNA

(c) (c) Genetic stability – according to Annex IIIa, II, A(10)
The stability in terms of genetic traits is expected to be equivalent to wild-type AAV. DNA of wild type AAV and of AAV-based vectors persists in transduced cells as circular (extrachromosomal) episomal concatemers in human tissues (Chen et al. 2005, Schnepp et al. 2005, Schnepp et al. 2009).
However, due to the lack of viral Rep and Cap genes, AAV5-hFIX is expected to remain in the cells as episomes and will not replicate and produce viral particles. The expression cassette will be transcribed and translated by host cell enzymes leading to expression of FIX.

4. Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?
Yes (X) No (.)
If yes, insert the country code(s) DE

5. Has the same GMO been notified for release elsewhere in the Community by the same notifier?
Yes (X) No (.)
If yes:
- Member State of notification DE
- Notification number B/../../… not yet available

Please use the following country codes:
Austria AT; Belgium BE; Germany DE; Denmark DK; Spain ES; Finland FI; France FR; United Kingdom GB; Greece GR; Ireland IE; Iceland IS; Italy IT; Luxembourg LU; Netherlands NL; Norway NO; Portugal PT; Sweden SE

6. Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?
Yes (.) No (X)
If yes:
- Member State of notification …
- Notification number B/../../…

7. Summary of the potential environmental impact of the release of the GMOs.
AAV5-hFIX is a recombinant, replication-deficient, adeno-associated virus-based vector that will be administered intravenously by a single dose infusion to severe or moderately severe haemophilia B patients. The intended application of AAV5-hFIX is limited to a few hospital centres and the number of patients to be treated is restricted. In addition, in view of the results obtained in non-human primates, a limited number of particles are expected to be

shed from the patients. Due to the extremely low numbers of AAV5-hFIX 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, AAV5-hFIX sequences would not confer a selective advantage to bacteria: AAV5-hFIX 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.

Due to the lack of viral Rep and Cap genes, the vector will persist as episome and will not replicate or produce viral particles. The expression cassette will be transcribed and translated by host cell enzymes leading to expression of the human factor IX protein.

Although human infections are common, wild type AAV is not known to be a pathogenic virus in humans and can be classified as a Risk Group 1 biological agent, defined in the EU as 'one that is unlikely to cause human disease' according to Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work.

Wild type AAV is not known to be involved in environmental processes and none of the genetic modifications made to wild type AAV during construction of AAV5-hFIX is expected to have any impact on this property. As such, there is no expected impact to the environment following the release of AAV5-hFIX.

Nonetheless, the hospital centres are expected to have adequately trained the health care professionals involved in the study in the safe handling of GMOs and to have best biosafety practices implemented in order to minimize any accidental exposure to the product, be it personnel, contact persons or the environment. In view of the low risk AAV5-hFIX presents to people and the environment and in view of the biorisk management measures applied to even further reduce the exposure to the vector, its overall risk for people and the environment can be evaluated as negligible.

B. Information relating to the recipient or parental organism from which the GMO is derived

1. Recipient or parental organism characterisation:

(a) Indicate whether the recipient or parental organism is a:

(select one only)

viroid	(.)		
RNA virus	(.)		
DNA virus	(X)		
bacterium	(.)		
fungus	(.)		
animal			
- mammals	(.)		
- insect	(.)		
- fish	(.)		
- other animal	(.)	(specify phylum, class)	…
other, specify	…		

2. Name

(i)	order and/or higher taxon (for animals)	N/A
(ii)	genus	Dependovirus
(iii)	species	Parvoviridae
(iv)	subspecies	Adeno-Associated Virus
(v)	strain	N/A
(vi)	pathovar (biotype, ecotype, race, etc.)	Serotype 5…
(vii)	common name	Adeno-associated virus or AAV

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:

Yes (X) No (.) Not known (.)

(b) Indigenous to, or otherwise established in, other EC countries:

(i) Yes (X)

If yes, indicate the type of ecosystem in which it is found:

Atlantic	(X)
Mediteranean	(X)
Boreal	(X)
Alpine	(X)
Continental	(X)
Macaronesian	(X)

(ii) No (.)

(iii) Not known (.)

(c) Is it frequently used in the country where the notification is made?

Yes (.) No (X)

(d) Is it frequently kept in the country where the notification is made?

Yes (.) No (X)

4. Natural habitat of the organism

(a) If the organism is a microorganism

water	(.)
soil, free-living	(.)
soil in association with plant-root systems	(.)
in association with plant leaf/stem systems	(.)
other, specify	Specific hosts are humans and non-human primates

(b) If the organism is an animal: natural habitat or usual agroecosystem: N/A

5. (a) Detection techniques
Quantitative Polymerase Chain Reaction (QPCR)

(b) Identification techniques
Quantitative Polymerase Chain Reaction (QPCR)

6. Is the recipient organism classified under existing Community rules relating to the protection of human health and/or the environment?

Yes (X) No (.)

If yes, specify

Adeno-associated viruses are not known to be associated with any pathogenic effect and thus are not assigned an Advisory Committee on Dangerous Pathogens (ACDP) category. Recombinant AAV-based vectors are usually classified as Biosafety Class 1 or 2 (depending on the Member State).

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?

Yes (.) No (X) Not known (.)

If yes:

(a) to which of the following organisms:

humans (.)
animals (.)
plants (.)
other (.)

(b) give the relevant information specified under Annex III A, point II. (A)(11)(d) of Directive 2001/18/EC

AAVs are frequently found in humans and animals, but they are not pathogenic, virulent, allergenic, or a carrier (vector) of a pathogen. The known host range includes humans and non-human primates. In natural conditions, wild type AAV is found to transmit to humans in the presence of a helper virus. It does not activate latent virus and is not able to colonise other organisms.

8. Information concerning reproduction

(a) Generation time in natural ecosystems:
Not applicable since the vector is not capable of replication.

(b) Generation time in the ecosystem where the release will take place:
Not applicable since the vector is not capable of replication.

(c) Way of reproduction: Sexual N/A Asexual N/A

(d) Factors affecting reproduction: Reproduction of wild-type AAV is dependent on co-infection with helper virus (Adenovirus or Herpesvirus)

9. Survivability

(a) ability to form structures enhancing survival or dormancy:

(i)	endospores	(.)
(ii)	cysts	(.)
(iii)	sclerotia	(.)
(iv)	asexual spores (fungi)	(.)
(v)	sexual spores (funghi)	(.)
(vi)	eggs	(.)
(vii)	pupae	(.)
(viii)	larvae	(.)
(ix)	other, specify	AAVs have the ability to form extrachromosomal concatemers that remain episomal for extended periods of time.

(b) relevant factors affecting survivability:
Replication of wild-type AAV is dependent on co-infection of helper viruses such as adenovirus or herpes-simplex virus. In presence of helper virus, AAV undergoes productive infection characterized by genome replication, viral gene expression and virion production. In absence of a helper virus co-infection, the virus DNA mainly remains as an extrachromosomal episome or may integrate into the host cell genome and in both cases the virus appears to remain latent.

10. (a) Ways of dissemination
Mainly through airway, although sexual transmission has been hypothesised.

(b) Factors affecting dissemination
Co-infection with a helper virus.

11. Previous genetic modifications of the recipient or parental organism already notified for release in the country where the notification is made (give notification numbers)
None

C. **Information relating to the genetic modification**

1. Type of the genetic modification

(i)	insertion of genetic material	(X)
(ii)	deletion of genetic material	(X)
(iii)	base substitution	(.)
(iv)	cell fusion	(.)
(v)	others, specify	…

2. Intended outcome of the genetic modification
The outcome of the genetic modifications is the deletion of the Rep and Cap viral sequences, leading to the loss of replication ability, and the insertion of the human factor XI transgene

expression cassette leading to the expression of hFIX in the transduced cells.

3. (a) Has a vector been used in the process of modification?

Yes (X) Baculovirus No (.)

If no, go straight to question 5.

(b) If yes, is the vector wholly or partially present in the modified organism?

Yes (.) No (X)

If no, go straight to question 5.

4. If the answer to 3(b) is yes, supply the following information

(a) Type of vector

plasmid (.)
bacteriophage (.)
virus (.)
cosmid (.)
transposable element (.)
other, specify …

(b) Identity of the vector

…

(c) Host range of the vector

…

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype

Yes (.) No (.)

antibiotic resistance (.)
other, specify …

Indication of which antibiotic resistance gene is inserted

…

(e) Constituent fragments of the vector

…

(f) Method for introducing the vector into the recipient organism

(i) transformation (.)
(ii) electroporation (.)
(iii) macroinjection (.)
(iv) microinjection (.)
(v) infection (.)
(vi) other, specify

5. If the answer to question B.3(a) and (b) is no, what was the method used in the process of modification?

(i) transformation (.)
(ii) microinjection (.)
(iii) microencapsulation (.)
(iv) macroinjection (.)
(v) other, specify Triple infection of *expresSF+* insect cells with baculovirus containing respectively the Rep, Cap or hFIX expression cassette sequences. Any remaining baculovirus are then removed by downstream processing.

6. Composition of the insert

(a) Composition of the insert
i) Inverted Terminal Repeats (ITRs) from AAV2
ii) LP1 promoter/enhancer element from the human apolipoprotein hepatic control region and the human alpha-1-antitrypsin promoter.
iii) Codon-optimised human factor IX expression cassette
iv) Bovine Growth Hormone polyA unit (pA bGH)

(b) Source of each constituent part of the insert
i) Inverted Terminal Repeats (ITRs): AAV2
ii) LP1 promoter/enhancer element: human
iii) Codon-optimised human factor IX expression cassette: human
iv) polyA unit (pA bGH): bovine

(c) Intended function of each constituent part of the insert in the GMO
i) Inverted Terminal Repeats (ITRs): Elements necessary for the packaging of the vector genome into the capsid and the formation of the episomal concatemers in the transduced cells.
ii) LP1 promoter/enhancer element: Enhance the expression of the transgene
iii) Codon-optimised human factor IX expression cassette: Active part of the vector needed for the expression of the human coagulation factor IX protein.
iv) polyA unit (pA bGH): mRNA translation

(a) Location of the insert in the host organism

- on a free plasmid (.)
- integrated in the chromosome (.)
- other, specify Mainly extrachromosomal by formation of episomal concatemers

(b) Does the insert contain parts whose product or function are not known?
Yes (.) No (X)
If yes, specify …

D. Information on the organism(s) from which the insert is derived

1. Indicate whether it is a:

	viroid	(.)
	RNA virus	(.)
	DNA virus	(.)
	bacterium	(.)
	fungus	(.)
	animal	
-	mammals	(.)
-	insect	(.)
-	fish	(.)
-	other animal	(.)
		(specify phylum, class) …
	other, specify	Human (coagulation factor IX cDNA)

2. Complete name

(i)	order and/or higher taxon (for animals)	Primates
(ii)	family name for plants	N/A
(iii)	genus	Homo
(iv)	species	Sapiens
(v)	subspecies	Sapiens
(vi)	strain	N/A
(vii)	cultivar/breeding line	N/A
(viii)	pathovar	N/A
(ix)	common name	Human

3. Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?

Yes (.) No (X) Not known (.)

If yes, specify the following:

(a) to which of the following organisms:

humans	(.)
animals	(.)
plants	(.)
other	..

(b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism

Yes (.) No (X) Not known (.)

If yes, give the relevant information under Annex III A, point II(A)(11)(d):

…

4. Is the donor organism classified under existing Community rules relating to the protection of human health and the environment, such as Directive 90/679/EEC on the protection of workers from risks to exposure to biological agents at work?

Yes (.) No (X)

If yes, specify …

5. Do the donor and recipient organism exchange genetic material naturally?

Yes (X) No (.) Not known (.)

Although following naturally acquired infection, AAV DNA mainly persists as circular double stranded episomes in human tissues (Schnepp *et al.*, 2005) it has been shown that some level of integration may occur in the host DNA (Kaeppel et al, 2013).

E. Information relating to the genetically modified organism

1. Genetic traits and phenotypic characteristics of the recipient or parental organism which have been changed as a result of the genetic modification

(a) is the GMO different from the recipient as far as survivability is concerned?

Yes (.) No (X) Not known (.)

Due to the removal of the Rep and Cap genes, AAV5-hFIX is replication incompetent even in the presence of wild-type AAV.

(b) is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?

Yes (X) No (.) Unknown (.)

Due to the removal of the Rep and Cap genes, AAV5-hFIX is replication incompetent even in the presence of wild-type AAV.

(b) is the GMO in any way different from the recipient as far as dissemination is concerned?

Yes (X) No (.) Not known (.)

The GMO cannot enter an infectious cycle even in the presence of helper function.

(c) is the GMO in any way different from the recipient as far as pathogenicity is concerned?

Yes (.) No (X) Not known (.)

Neither wild type AAV nor AAV5-hFIX are pathogenic to humans or the environment.

2. Genetic stability of the genetically modified organism

AAV5-hFIX is replication incompetent. In absence of an intrinsic mechanism for genetic variation or instability and based on the known genetic stability of wild type AAV, the genetic traits of the organism are expected to be stable.

3. Is the GMO significantly pathogenic or harmful in any way (including its extracellular products), either living or dead?

Yes (.) No (X) Unknown (.)

(a) to which of the following organisms?

humans	(.)
animals	(.)
plants	(.)
other	N/A

(b) give the relevant information specified under Annex III A, point II(A)(11)(d) and II(C)(2)(i)

Humans are likely infected by wild type AAV through the respiratory tract, sexual and gastrointestinal route. AAV is capable of infecting either non-dividing or dividing cells.
In the presence of helper virus (adenovirus or herpes virus), AAV undergoes productive infection characterized by genome replication, viral gene expression and virion production.
In the absence of a helper virus co-infection, AAV DNA remains extrachromosomal or may integrate in the host DNA. In both situations the virus remains latent.
Wild type AAV is weakly immunogenic. AAV-induced immune reaction is seemingly restricted to the generation of neutralizing antibodies.
AAV has never been associated with any disease or pathological conditions in humans. AAV is not known to be associated to plants. AAV5-hFIX is not expected to be pathogenic and does not interfere with any prophylactic or therapeutic treatments since it does not contain any sequences (no antibiotic-resistance genes) that could affect prophylaxis or treatment of pathogenic microorganism infection.

The hFIX cDNA present in the vector is a naturally occurring sequence in healthy humans. Expression of this protein by infected cells does not induce cytopathic effects.

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment
The number of vector genomes can be determined by quantitative PCR with primers specific for vector sequences. This technique however is only applicable where sufficient DNA can be recovered for analysis.

(b) Techniques used to identify the GMO
The vector is identified by quantitative PCR with primers specific for vector sequences.

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)
The purpose of the release is a clinical study designed as a single-dose, dose-escalation, multi-centre trial investigating the safety and efficacy of the intravenous administration of AAV5-hFIX to severe haemophilia B patients. No environmental benefit is expected.

2. Is the site of the release different from the natural habitat or from the ecosystem in which the recipient or parental organism is regularly used, kept or found?

Yes (X) No (.)

If yes, specify: The GMO will be administered intravenously to Haemophilia B patients in a few hospital centres. Shedding of vector DNA in urine, saliva or faeces can be expected afterwards for a few days, however shed AAV-based vectors have been shown to be non-infectious.

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference):
University Medical Centre Groningen
Division of Thrombosis and Haemostasis
Department of Haematology
Hanzeplein 1
9713 GZ Groningen
The Netherlands

(b) Size of the site (m^2): N/A m^2
(i) actual release site (m^2): … m^2
(ii) wider release site (m^2): … m^2

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:
Not applicable considering that shed material, if any at all, is non-infectious.

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO
None.

4. Method and amount of release

(a) Quantities of GMOs to be released:
A total of 10 patients are anticipated to be enrolled in the proposed clinical study in two cohorts of 5 patients each. It can be expected that a maximum of 2 to 4 patients will be treated at the proposed site. The proposed dose range is $5x10^{12}$ gc/kg (cohort 1) and $2x10^{13}$ gc/kg (cohort 2). Assuming a maximum case of 4 patients treated in the highest dose group at the same site, the total amount of vector at that site would be around $6.4x10^{15}$ genome copies.
Some shedding of vector DNA is expected to occur in body fluids/excreta for several days after administration. In urine, representing the largest volume of excreta, vector DNA amounts around $1/10^{10}$ of the dose can be expected to be shed during the first days after administration to the patients.

(b) Duration of the operation:
The complete administration procedure including preparation of the infusion system is expected to take less than 24h. The maximum DNA shedding duration after treatment in animal studies did not exceed a few days.

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release

The investigational medicinal product will be supplied to the selected hospital centres on a subject-to-subject basis following confirmation of subject's eligibility, in order to avoid any long time storage.
All involved personnel on the site will be trained in best biosafety practices to be applied during preparation in the pharmacy, transport to the administration room, precautions during administration and disposal of any biological waste. Such training involves, among others, wearing adapted protective clothing, gloves and goggles, the constant presence of a spill kit and the decontamination of waste prior to disposal.

5. Short description of average environmental conditions (weather, temperature, etc.)
Hospital treatment room, ambient indoor conditions for administration to clinical trial subjects. Receiving environment for the shed vector particles is most likely waste water and ambient temperature. The investigational medicinal product should be stored at -20°C ± 5°C until administration.

6. Relevant data regarding previous releases carried out with the same GMO, if any, specially related to the potential environmental and human health impacts from the release.
None available.

G. Interactions of the GMO with the environment and potential impact on the environment, if significantly different from the recipient or parent organism

1. Name of target organism (if applicable)

(i)	order and/or higher taxon (for animals)	Primates
(ii)	family name for plants	N/A
(iii)	genus	Homo
(iv)	species	Sapiens
(v)	subspecies	Sapiens
(vi)	strain	N/A
(vii)	cultivar/breeding line	N/A
(viii)	pathovar	N/A
(ix)	common name	Human

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)
In treated subjects, AAV5-hFIX is expected to preferentially localise to the liver. Hepatocytes transduction will enable a functional human coagulation factor IX to be expressed. The excretion of functional factor IX into the circulation at levels resulting in a clinically meaningful improvement in the clotting function will improve the haemophilia phenotype of the patients. The vector DNA is expected to persist in transduced cell by the formation of episomal concatemers.

3. Any other potentially significant interactions with other organisms in the environment
None expected for this product.

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?
Yes (.) No (X) Not known (.)

Give details

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established

Even in the event of shedding of DNA in waste water no establishment in such a system can be expected.

6. Complete name of non-target organisms which (taking into account the nature of the receiving environment) may be unintentionally significantly harmed by the release of the GMO

None.

(i) order and/or higher taxon (for animals) …

(ii) family name for plants …

(iii) genus …

(iv) species …

(v) subspecies …

(vi) strain …

(vii) cultivar/breeding line …

(viii) pathovar …

(ix) common name …

7. Likelihood of genetic exchange in vivo

(a) from the GMO to other organisms in the release ecosystem: Highly unlikely.

Due to the low numbers of vector DNA copies potentially released into the environment through shedding, horizontal gene transfer is highly unlikely. Even if horizontal gene transfer occurred, the sequences would not confer a selective advantage to other organisms such as bacteria since AAV-hFIX 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 AAV5-hFIX 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.

(b) from other organisms to the GMO: Highly unlikely.

Since AAV5-hFIX contains the ITR-sequences of AAV2, there is a (remote) possibility of homologous recombination of the vector with wild type AAV2 in case of a co-infection in exposed persons. The result of such a recombination would be that AAV5-hFIX 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 replication incompetent.

(c) likely consequences of gene transfer:

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. Any recombination would result in the expression of hFIX by infected cells.

8. Give references to relevant results (if available) from studies of the behaviour and characteristics of the GMO and its ecological impact carried out in stimulated natural environments (e.g. microcosms, etc.):
No references available.

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)
None known or predictable since wild type AAV is not known to be involved in any biogeochemical process.

H. Information relating to monitoring

1. Methods for monitoring the GMOs
Collection of body fluids according to clinical protocol and risk management plan and quantification using a specific DNA QPCR method.

2. Methods for monitoring ecosystem effects
No monitoring is considered necessary.

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
The method for detecting transfer of the donated genetic material to other organisms will be QPCR. The presence of vector DNA sequences will be determined in serum, urine, faeces, saliva and semen from the treated patients. However, it has been shown that the material found in excreta is not infectious and thus transfer of donated genetic material from the patient to other organisms is not envisaged.

4. Size of the monitoring area (m^2)
Not applicable. Only subject's body fluids will be monitored after administration.

5. Duration of the monitoring
The body fluids of the treated subjects will be monitored until found negative (three consecutive negative samples) for the presence of vector DNA.

6. Frequency of the monitoring
At regular intervals according to clinical protocol (e.g. once weekly for the first three months depending on the nature of the sample) for five years after administration.

I. Information on post-release and waste treatment

1. Post-release treatment of the site

Decontamination of the IMP administration room by standard procedures will be used after administration. Any material or surface in contact with the product will be decontaminated with 10% bleach solution (allowing contact for at least 10 minutes) or autoclaved.
Any other disposable instruments or other materials used during the dose preparation procedure will be disposed of in a manner consistent with the standard practice of the institution for potentially biohazardous materials.

2. Post-release treatment of the GMOs

Since the product will be supplied by the manufacturer to the hospital pharmacy in a subject-to-subject manner, no unused product should remain at the hospital centre after administration of the patients. Any open vials or unused material will be destroyed by decontamination according to local biosafety guidelines.

3. (a) Type and amount of waste generated

Empty vials and used vials and the used delivery system components (guide tube, cannula, injection needles and syringes), gauzes, personal protective equipment (e.g. gloves etc) and components used for collecting body fluids samples after administration.

(b) Treatment of waste

Sharps such as needles will be disposed of in adequate sharp containers and incinerated.
Disposables such as syringes, tubing and catheters will be decontaminated by immersion in a chemical disinfectant with virucidal activity before incineration.
All the surgical materials (surgery tools, linens) and surgery waste (gloves, compresses) will be collected and autoclaved before washing and sterilization or incineration. All non-disposable surgical equipment will be cleaned using a chemical disinfectant with proven virucidal activity (e.g. hypoclorite solution) and then sterilized by autoclaving according to standard practice of the institution.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread

The solution of AAV5-hFIX for intravenous infusion will be prepared by the hospital pharmacist or designee in a contained area inside a flow cabinet in the hospital centres. In case of spillage the affected area, lineated with absorbing material, will be decontaminated using appropriate disinfectants. A spill kit will be available at all times during the administration procedure. Details are given in the IMP Handling Manual, describing the handling of the IMP in the pharmacy and the administration procedures) that will be handed over to the sites during the site initiation visit (prior to starting the study).

2. Methods for removal of the GMO(s) of the areas potentially affected

For splashes to the eye of the GMO, rinse eye with eyewash for 15 minutes then report to hospital emergency room for evaluation. In case of accidental injection of material contain-

ing the GMO, wash area well with soap and water and report to hospital emergency room for evaluation.

In case of spills: allow aerosols to settle; wear protective clothes and goggles and gently cover the spill with adsorbent paper towel and apply freshly prepared 10% bleach starting at the perimeter and working towards the centre; allow at least 10 minutes contact time before clean up.

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread

Not applicable since exposure of plants or animals is not expected.

4. Plans for protecting human health and the environment in the event of an undesirable effect

No undesirable effects are expected.