SNIF: GMOB-2023-17331

Domain:
GMO

Authorisation type:
Deliberate release of GMO or a combination of GMOs for any other purpose than for placing on the market

Application type:
Summary notification for the release of genetically modified higher organisms other than higher plants in line with Decision 2002/813/EC Annex, Part 1.

Recipient Member State:
Netherlands

Competent Authority:
Ministry of Infrastructure and Water Management

Notification number:
B/NL/23/011

Acknowledgement date:
2023-07-06

A- General information

Details of notification

Details of notification
IM-MV 23-011
Member State of notification
Netherlands
Title of the project
Evaluation of safety and efficacy of an intravenous injection of GNT0003, a suspension of recombinant AAV8 viral vector carrying the human UGT1A1 transgene, in patients with Crigler-Najjar syndrome.
Proposed period of release
Starting date
2023-08-18
Finishing date
2030-12-01

Notifier

Name of institute or company
Academic Medical Center of the University of Amsterdam
Email
Not provided
Phone number
Not provided
Website
Not provided
Address
Not provided
Post code
Not provided
Country
Netherlands

GMO characterisation

(a) Indicate whether the GMO is a:

Viroid
No
RNA virus
No
DNA virus
Yes
Bacterium
No
Fungus
No
Animal
No

Other
No

(b) Identity of the GMO (genus and species)

Order: Parvoviridae; Genus: Dependoparvovirus; Species: Adeno-associated virus (AAV)

(c) Genetic stability - according to Annex IIIa, II, A(10)

Since GNT0003 is an Investigational Medicinal Product, stability testing programs are in place to monitor its stability.

Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?

Yes
Country
France
Italy

Has the same GMO been notified for release elsewhere in the Community by the same notifier?

Yes
Member State of notification
FR
Insert the notification number(s) (if exist)
Not applicable
Member State of notification
IT
Insert the notification number(s) (if exist)
Not applicable

Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?

No

Summary of the potential environmental impact of the release of the GMOs.

Environmental impact of GNT0003 is considered negligible. Specific measures are taken to avoid the GMO to be in contact with people other than the patient during the preparation and administration procedure. Even if accidental exposure occurs, the GMO is a replication-defective viral particle which would not be able to spread in the environment

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

1. Recipient or parental organism characterisation

Indicate whether the recipient or parental organism is a:

Viroid
No
RNA virus
No
DNA virus
Yes
Bacterium
No
Fungus
No
Animal
No
Other
No

2. Name

(i) Order and/or higher taxon (for animals)
Parvoviridae
(ii) Genus
Dependoparvovirus
(iii) Species
Adeno-associated virus (AAV)
(iv) Subspecies
Not applicable
(v) Strain
AAV2/8 or AAV8 ITRs present in the vector genome are derived from AAV serotype 2 The capsid consists of a capsid of AAV serotype 8
(vi) Pathovar (biotype, ecotype, race, etc.)
Not Applicable

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:
yes
(b) Indigenous to, or otherwise established in, other EC countries:
yes
Indicate the type of ecosystem in which it is found:
atlantic
mediterranean
boreal
alpine
continental

macaronesian
(c) Is it frequently used in the country where the notification is made?
Yes
(d) Is it frequently kept in the country where the notification is made?
Yes

4. Natural habitat of the organism

(a) Is the organism a microorganism ?
Yes
Water
No
Soil, free-living
No
Soil in association with plant-root systems
No
In association with plant leaf/stem systems
No
In association with animals
No
Other
Yes
Specify
primate
(b) Is the organism an animal?
No

5(a) Detection Techniques

Detection Techniques
Genome sequencing, qPCR

5(b) Identification Techniques

Identification Techniques
Genome sequence: qPCR and sequencing; Capside Proteins: SDS PAGE & Western Blot

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

Yes
Specify
There is no known link between AAV and any known human illness. Classification of AAV varies across different EU countries according to national regulatory guidelines: either Biosafety Level 1 or Biosafety Level 2.

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

no

8. Information concerning reproduction

(a) Generation time in natural ecosystems:
After entry into the host cell nucleus, WT AAV can follow either one of two distinct and interchangeable pathways of its life cycle: the lytic or the latent phase. For entry into a lytic phase, a latently infected cell need to be super-infected with a helper virus, inducing genome rescue of the provirus DNA followed by replication and packaging of the viral genome. Finally, upon helper virus-induced cell lysis, the newly assembled virions are released.
(b) Generation time in the ecosystem where the release will take place:
Not relevant. GNT0003 is a replication defective viral vector.
(c) Way of reproduction
Asexual
(d) Factors affecting reproduction:
Reproduction of WT AAV is dependent on co-infection with helper virus such as Adenovirus, vaccinia virus, herpes simplex virus, cytomegalovirus or human papillomavirus.

9. Survivability

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

(i) endospores
No
(ii) cysts
No
(iii) sclerotia
No
(iv) asexual spores (fungi)
No
(v) sexual spores (fungi)
No
(vi) eggs
No
(vii) pupae
No
(viii) larvae
No
Other
Yes
Specify
No
(b) Relevant factors affecting survivability
Since AAV is not pathogen, its stability has not been investigated in details. WT AAV is a small non enveloped virus with a stable capsid. Its half-life is expected to be long but can be rapidly inactivated under standard chemical or physical denaturating condition.

10(a) Ways of dissemination

The ways of dissemination for WT AAV are poorly understood, but is likely to occur through inhalation of aerosolized droplets, mucous membrane contact, parenteral injection, or ingestion.
10(b) Factors affecting dissemination
WT AAVs are not able to replicate unless a co-infection with a helper virus occurs

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)

Not Applicable

C. Information relating to the genetic modification

1. Type of the genetic modification

Insertion of genetic material
Yes
Deletion of genetic material
Yes
Base substitution
No
Cell fusion
No
Other
No

2. Intended outcome of the genetic modification

The transferred gene is a codon optimized human UGT1A1 transgene. The UGT1A1 transgene is intended to restore liver UGT1A1 enzyme activity to normalize bilirubin metabolism.

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

Yes
3(b) If yes, is the vector wholly or partially present in the modified organism?
No

6. Composition of the insert

(a) Composition of the insert

The insert contains the following elements: ApoE/AAT hybrid promoter, Intronic sequence of the human hemoglobin subunit beta-2 (HBB2), The ORF containing the cDNA sequence encoding a codon-optimized version of the hUGT1A1 gene; under the control of the hybrid promoter ApoE/AAT, Polyadenylation sequence of the human hemoglobin subunit beta 2 gene (HBB pA)

(b) Source of each constituent part of the insert

Human ApoE/AAT hybrid promoter: human; Intronic sequence HBB2: human; Transgene hUGT1A1: human; HBB pA signal: human

(c) Intended function each constituent part of the insert in the GMO

Human ApoE/AAT hybrid promoter: liver specific expression of the transgene; Intronic sequence HBB2: mRNA stabilisation; Transgene hUGT1A1: UGT1A1 expression in transduced hepatocytes; HBB pA signal: mRNA stabilisation

(d) Location of the insert in the host organism

On a free plasmid
No

Integrated in the chromosome
No
Other
Yes
Specify
With respect to the viral vector, the insert is between the inverted terminal repeats. With respect to the patient, the GMO is mainly extra chromosomal by formation of episomal concatemers.

(e) Does the insert contain parts whose product or function are not known?

No

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

1. Indicate whether it is a:

Viroid
No
RNA virus
No
DNA virus
No
Bacterium
No
Fungus
No
Animal
Yes

Select from following options:

Mammal
Yes
Insect
No
Fish
No
Other animal
No
Other
No

2. Complete name

(i) Order and/or higher taxon (for animals)
Primates
(ii) Family name (for plants)
Not applicable
(iii) Genus
Homo
(iv) Species
Homo Sapiens
(v) Subspecies
Not Applicable
(vi) Strain
Not Applicable
(vii) Cultivar/Breeding line
Not Applicable
(viii) Pathovar
Not Applicable
(ix) Common name
Human

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

no

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

no

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

Not Applicable

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 related to exposure to biological agents at work?

No

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

no

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?
no
Specify
The survivability of the recombinant AAV is not expected to be different from the wild-type virus
(b) Is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?
yes
Specify
The rAAV genome lacks Rep and Cap gene sequences and is therefore replication defective even in the presence of a helper virus.
(c) Is the GMO in any way different from the recipient as far as dissemination is concerned?
yes
Specify
The rAAV genome lacks Rep and Cap gene sequences and is therefore replication defective even in the presence of a helper virus.
(d) Is the GMO in any way different from the recipient as far as pathogenicity is concerned?
no
Specify
Neither the wild type AAV nor the GMO are pathogenic to humans or the environment.

2. Genetic stability of the genetically modified organism

The risk of modification of the genetic sequence is related to DNA synthesis errors which occur during vector replication. As the GMO is not replicative, no modification of the vector genome can occur. The production process is designed to minimize the formation of replication-competent viral particle. Once administrated in the patient, the formation of replication competent viral particle transporting the therapeutic cassette is considered highly unlikely mainly because 1) it would require an infection with a helper virus and a WT AAV 2) the packaging efficiency is profoundly affected during packaging of DNA above 5kb.

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

no
(b) Give the relevant information under Annex III A, point II (A)(11)(d) and II(C)(2)(i):
Not Applicable

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment
PCR with primers specific of the recombinant viral DNA
(b) Techniques used to identify the GMO
Molecular identity: PCR and sequence analysis; Viral Protein identity: Western Blot

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)

The objective of the clinical study is to evaluate safety and efficacy of an administration of an investigational medicinal product (IMP), GNT0003, intended to treat congenital unconjugated hyperbilirubinemia (Crigler-Najjar syndrome), an ultra-rare liver disorder affecting 1 in a million newborns. Crigler-Najjar (CN) syndrome is caused by mutations in the UGT1A1 gene which codes for the 1A1 isoform of the Uridine diphosphate Glucuronosyl Transferase (UGT1A) enzyme family. UGT1A1 deficiency results in life threatening accumulation of unconjugated bilirubin, a neurotoxic metabolite. Delivering correct UGT1A1 gene to the liver using GNT0003 is expected to restore bilirubin conjugation thereby restoring the excretion and preventing brain damage caused by high serum levels of unconjugated bilirubin.

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?

No

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference):

The clinical trial will be conducted at a single investigational site in the Netherlands: Academic Medical Center of the University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam

(b) Size of the site (m2)

(i) actual release site (m2)
Not Applicable
(ii) wider release area (m2)
Not Applicable

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:

Not Applicable

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO

Not Applicable

4. Method and amount of release

(a) Quantities of GMOs to be released:

A maximal dose of 2E+13 vector genome / kg will be administrated. The IMP will be administered once during the course of the Clinical Trial.

(b) Duration of the operation:

Administration consists of an intravenous injection during a maximum of 2 hours to each patient followed by an observation period of about 24 hours.

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

The clinical trial subject to this submission will be conducted in a unique clinical trial site in The Netherlands: The Academic Medical Center of the University of Amsterdam. The GMO will be supplied to the hospital pharmacy as frozen aliquot stored in dry ice, by a courier accredited for the transport of biological products including GMOs. Further storage of the GMO will take place in a monitored freezer placed in the Academic Medical Center pharmacy premises in a room with restricted access. The preparation of the GMO will be done at the pharmacy in a class II biosafety cabinet the day of administration. To avoid the risk of injury with needle, plastic spikes will be used to remove the GMO from the primary container and transfer it into the infusion bag. The prepared infusion bag will be transferred from the pharmacy to the department of gastroenterology and hepatology in a sealed container to limit accidental dissemination Patient will be treated and hospitalized in a room by a medical professional. All standard precautions to prevent aerosol formation and spills will be applied and will prevent exposure of the ward and personal. All disposable waste that has been or could have been in contact with the GMO or was actively used at the time of preparation or administration of the GMO will be disposed of in bins dedicated to contain specific hospital waste and GMOs. Bins will be securely closed within the contained area, decontaminated at the outside using a 1000 ppm chloride solution and labeled GMO waste. Closed labelled bins will be transported to the logical exit point of the hospital where the bins are handed over to the company which will transport the bins from the hospital to the waste destruction company. All other putatively contaminated items will be autoclaved or decontaminated using 1000 ppm chloride. All involved personnel on the site will be trained and will use protective clothing, gloves and googles/face shield.

5. Short description of average environmental conditions (weather, temperature etc.)

The clinical trial will take place in the Netherlands which has a temperate climate. The risk of release of GNT0003 in the environment is unrelated to climatic characteristics.

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

No known risk was detected during previous release in Community (FR & IT).

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 organisms (if applicable)

Applicable?
Yes
(i) Order and/or higher taxon (for animals)
Primates
(ii) Family name (for plants)
Not Applicable
(iii) Genus
Homo
(iv) Species
Homo Sapiens
(v) Subspecies
Not Applicable
(vi) Strain
Not Applicable
(vii) Cultivar/Breeding line
Not Applicable
(viii) Pathovar
Not Applicable
(ix) Common name
Human

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)

Applicable?
Yes
Specify
After administration to patients, the GMO is expected to transfer the codon-optimized human UGT1A1 transgene under the control of a liver specific promoter in patients cells with a strong liver tropism. The UGT1A1 transgene is intended to restore liver UGT1A1 enzyme activity to normalize metabolism

3. Any other potentially significant interactions with other organisms in the environment

No interaction with other organisms in the environment is anticipated

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?

no

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

WT AAV8 is not known to infect any other organisms in the environment except primates. The recombinant vector being unable to replicate, even in the presence of a helper virus, the consequence of an infection would be negligible.

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

(i) Order and/or higher taxon (for animals)
Not Applicable
(ii) Family name (for plants)
Not Applicable
(iii) Genus
Not Applicable
(iv) Species
Not Applicable
(v) Subspecies
Not Applicable
(vi) Strain
Not Applicable
(vii) Cultivar/Breeding line
Not Applicable
(viii) Pathovar
Not Applicable
(ix) Common name
Not Applicable

7. Likelihood of genetic exchange in vivo

(a) from the GO to other organisms in the release ecosystem:
WT AAV8 is not known to infect any other organisms in the environment except primates.
(b) from other organisms to the GMO:
Not anticipated
(c) likely consequences of gene transfer**
Successful transduction after IMP administration will result in UGT1A1 protein expression in the liver. This will restore the conversion of unconjugated bilirubin in non-toxic bilirubin glucuronides that are excreted into the bile. If effective this will prevent accumulation of unconjugated bilirubin in blood and brain.

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 simulated natural environments (e.g. microcosms etc.):

To date, no specific studies on the potential ecological impact of GNT0003 have been performed. However, as GNT0003 can only transduce animal cells and is non-replicative, dispersal will be limited to the first organism infected and therefore there is no potential for population increase within the environment. The vector is not expected to survive anywhere in the natural environment.

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)

Not Applicable

H. Information relating to monitoring

H. Information relating to monitoring

1. Methods for monitoring the GMOs
The presence of vector genome sequences in patients biological fluids will be monitored using quantitative PCR (qPCR).
2. Methods for monitoring ecosystem effects
Not applicable.
3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
Not applicable.
4. Size of the monitoring area (m2)
Not applicable.
5. Duration of the monitoring
Biological fluids will be collected and tested until at least two consecutive samples are negative.
6. Frequency of the monitoring
The monitoring will be done regularly until at least to two consecutive samples are negative.

I. Information on post release and waste treatment

I. Information on post release and waste treatment

1. Post-release treatment of the site
All waste generated (material in contact with the GMO during the IMP preparation and administration) will be disposed as biohazard waste; other items that might have come into contact with the GMO will be autoclaved or decontaminated using a 1000 ppm chloride solution.
2. Post-release treatment of the GMOs
All waste generated (material in contact with the GMO during the IMP preparation and administration) will be disposed as biohazard waste; other items that might have come into contact with the GMO will be autoclaved or decontaminated using a 1000 ppm chloride solution.
3(a) Type and amount of waste generated
GMO waste from the pharmacy will consist of vials, tubing, syringes, needles, gloves, gowns etc. GMO waste from the patient ward will consist of infusion bag, tubing and related accessories, gloves, gowns etc.
3(b) Treatment of waste
Bins containing GMO waste will be securely closed within the contained area, decontaminated at the outside using a 1000 ppm chloride solution and labeled GMO waste. Closed labelled bins will be transported to the logical exit point of the hospital where the bins are handed over to the company which will transport the bins from the hospital to the waste destruction company.

J. Information on emergency response plans

J. Information on emergency response plans

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

In case of incident while handling the GMO the actions recommended are described in the Pharmacy Guide. All of the people involved in the clinical trial will be trained about the procedures and measures to be taken in case of accidental release. In case of unexpected spread, the GMO spill should be contained with an appropriate solution of chloride solution on paper towel: Handle with individual protective equipment : gloves, mask, gowns and safety glasses Cover the spill area with paper towel Soak with 1000 p.p.m. chloride solution After 20 minutes, clean the zone starting by the outside of the zone to the inside and destroy contaminated items by autoclaving and incineration. Remove traces of disinfectant from the spill by wiping the surface intensively with 70% alcohol.

2. Methods for removal of the GMOs of the areas potentially affected

See 1.

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

Not Applicable

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

Pharmacovigilance system will collect all individual adverse events. Considering the negligible risk for the environment, no specific plans for protecting the environment are deemed necessary.