SNIF: GMOB-2026-37460

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: Belgium

Competent Authority: Federal Public Service of Health, Food Chain Safety and Environment (FPS HFCSE)

A- General information

Details of notification

Details of notification GMO application

Member State of notification Belgium

Title of the project Phase 1/2 Investigation Of Novel Experimental Regimen in Amyotrophic Lateral Sclerosis (PIONEER-ALS): An Open-Label, Uncontrolled, Multicenter Study to Assess the Safety and Tolerability of Two Doses of VTx-002

Proposed period of release

Starting date 2025-12-12

Finishing date 2027-12-31

Notifier

Name of institute or company Vectory Therapeutics b.v

Email ilan.mcnamara@vectorytx.com

Phone number +12158739963

Website Not provided

Address Science Park, Matrix Innovation Center 408 Amsterdam

Post code 1098 XH

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)

Family: Parvoviridae, Genus: Dependovirus, Specie: Adeno-associated virus (AAV) serotype 5

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

AAV vectors are replication incompetent and will not replicate in vivo, therefore genetic stability is not relevant for AAV-based gene therapy vectors. Nevertheless, the absence of replication competent AAV in the VTx-002 final product is confirmed using a GMP qualified method at a sensitivity of 20 IU/1E11 viral genomes. Furthermore, the genetic identity and integrity of the clinical batch has been confirmed by Sanger sequencing and NGS (Illumina and PacBio).

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

Yes

Country Netherlands Belgium Spain United Kingdom

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

No

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

Yes

Country United States

Notification number IND 031923

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

Environmental Risk Assessment for VTx-002 GMO Release The environmental risk associated with this GMO release is negligible. The vector is replication-deficient, eliminating any potential for autonomous spread in the absence of both a helper virus and AAV Rep/Cap genes, which are not present under clinical conditions. Furthermore, even in the highly improbable scenario of co-infection with a helper virus and replication-competent wild-type AAV, recombination to generate a replicative AAV is precluded by the genetic design of the VTx-002 genome. Extensive experience from hundreds of AAV-based clinical trials consistently demonstrates negligible environmental risk, attributable to replication incompetence and absence of helper virus. Supporting data from shedding studies and biodistribution analyses of similar AAV5-based products confirm minimal dissemination and no capacity for environmental amplification. Interaction with Non-Target Organisms No significant interaction with non-target organisms is anticipated: · AAV is non-pathogenic and has not been associated with disease in humans or ani-mals. · The vectorized transgene is expressed intracellularly and does not confer traits that enhance survival, persistence, or invasiveness in environmental ecosystems. · There is no mechanism for selective advantage, and the vector

cannot compete or es-tablish in any ecological niche due to replication deficiency and lack of transmissibility. Containment and Biosafety Measures Clinical administration occurs under controlled conditions with standard biosafety protocols. Waste disposal follows GMO-specific procedures to prevent accidental environmental exposure. Shedding and Environmental Exposure Based on prior AAV5 clinical trials (e.g., Hemgenix, Roctavian), shedding into bodily fluids is transient and at very low levels, posing negligible risk to contacts or the environment. Vector shedding for VTx-002 was evaluated in non-human primates in the GLP Toxicology study. Doses higher than the intended clinical dose (gc/animal) were delivered using the same route of administration as the proposed clinical study. Shedding analysis by qPCR indicated that vector was rapidly cleared from the CSF, with levels dropping below the lower limit of quantification by Day 90. Vector genomes in feces and urine were not detected after the first month post-dosing. The clinical protocol VTx-002-01-001 includes a comprehensive viral shedding assessment to monitor potential excretion of VTx-002 following administration to capture both early and delayed shedding. Participants will receive instructions on safe handling of body fluids, and clinical sites will implement environmental precautions to mitigate any associated risks. As VTx-002 is administered to study subjects under controlled conditions via a single injection, the most likely route of biological dispersal is via shedding. It is not expected that exposure to the amount of vector anticipated to be shed, even if it were infectious, would result in any biologically significant level of transduction. This assumption is based on the fact that the amount of vector shed is anticipated to be several orders of magnitude lower than the lowest effective dose and that effective delivery is by an intra cisterna magna route. Furthermore, the very low amount of vector particles would be inactivated by the skin’s function as a physical barrier against infection. Thus, the low levels of vector that may be shed over a short period of time are not expected to present a safety concern for the general human population or the environment. Other than potential human hosts, exposure to VTx-002 is not expected to affect any non-target organisms, either directly or indirectly. The vector is replication-incompetent and is not expected to survive, multiply, or disperse following its release during the proposed clinical study

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) TBC

(ii) Genus Dependovirus

(iii) Species Adeno-associated virus (AAV)

(iv) Subspecies Serotype 5

(v) Strain Not Applicable

(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: continental

(c) Is it frequently used in the country where the notification is made? No

(d) Is it frequently kept in the country where the notification is made? No

4. Natural habitat of the organism

(a) Is the organism a microorganism ? No

(b) Is the organism an animal? No

5(a) Detection Techniques

Detection Techniques Enzyme linked Immunosorbent Assay (ELISA); Polymerase Chain Reaction (PCR)

5(b) Identification Techniques

Identification Techniques Enzyme linked Immunosorbent Assay (ELISA); Polymerase Chain Reaction (PCR)

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

Yes

Specify Wild-type AAV is not classified in Risk Groups 2, 3 or 4 according to Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work (Annex III of the Directive). It is designated a Risk Group 1 biological agent, defined in the EU as 'one that is unlikely to cause human disease'

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: Wild-type AAV requires the co-infection of a helper virus to enable replication (trait of the Dependovirus family). Replication in an infected host can take from 24 to 48 hrs but does not occur in the absence of an appropriate helper virus. The VTx-002 rAAV vector cannot replicate in the presence of a helper virus as it lacks the AAV Rep and Cap genes required for replication.

(b) Generation time in the ecosystem where the release will take place: Not applicable since the vector is not capable of replication even in the presence of a helper virus as it lacks the rep and cap genes required for rescue/packaging.

(c) Way of reproduction Asexual

(d) Factors affecting reproduction: Reproduction of wild-type AAV is dependent on co-infection with helper virus (e.g., adenovirus or herpesvirus). Furthermore, AAV Rep and Cap sequences must be present to allow replication of the viral genome. The VTx-002 GMO vector does not contain any of the wtAAV genes essential for DNA replication and DNA packaging into the AAV particle. Therefore, the GMO is not capable of replication regardless of presence of helper virus.

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 AAV does not form survival structures. In the latent form. The vector DNA genome has the ability to form extrachromosomal concatemers that remain episomal for extended periods of time, however this is as DNA and not in form of infectious or replicative virus.

(b) Relevant factors affecting survivability Wild-type AAV is a non-enveloped virus, with a stable capsid. There have been extensive studies on AAV vectors showing that exposure to heat, UV radiation, or extreme pH can inactivate recombinant vector particles. For example, AAV particles are resistant pH 3 to 9 and can resist heating at 56 C for 1 hour (Berns and Bohenzky, 1987). None of the genetic modifications made to VTx-002 are expected to have an effect on the mode of transmission, survivability in the environment, or sensitivity to inactivating agents.

10(a) Ways of dissemination

10(a) Ways of dissemination Wild-type AAV is thought to be spread in nature via inhalation of aerosolized droplets, mucous membrane contact or ingestion.

10(b) Factors affecting dissemination Co-infection with a helper virus. However, the GMO is not capable of replication regardless of the presence of a helper virus. Environmental conditions which may affect survival of the GMO outside the host are temperature, pH and environmental humidity.

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 intended outcome of the modifications was to remove the entire Replicase and Capsid genes from the WT AAV genome and replace this with the therapeutic transgene cassette of VTx-002. The only remaining viral elements are the inverted terminal repeats (ITRs) which are necessary for production and packaging of the recombinant AAV gene therapy vector. These ITRs do not encode proteins or any viral elements, they are DNA regulatory sequences.

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

Composition of the insertion fragment: The VTx-002 expression cassette comprises two AAV2-ITRs that flank the promotor, an intron, the coding transgene sequence and a polyadenylation signal.

(b) Source of each constituent part of the insert

ITRs: AAV2 derived; Promoter: Fully Human; Intron: Human/Synthetic chimeric; Therapeutic transgene – Humanized coding sequence; Polyadenylation signal – viral (simian virus 40)

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

AAV2-ITR: genome replication and capsid packaging; Promotor: To initiate transcription of the therapeutic transgene Intron: Enhance transgene expression Therapeutic transgene: to treat disease in the recipient; Polyadenylation signal: post transcription regulatory element mRNA polyadenylation and stability

(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 recipient patient, the vector genome is localized mainly extrachromosomally 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) Homo

(iii) Genus Homo Sapiens

(iv) Species N/A

(v) Subspecies N/A

(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?

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 n/a

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?

yes

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 If anything the GMO has reduced survival capacity as it is replication incompetent and does not contain any of the wild type AAV genes required for replication (in the presence of a helper virus). The VTx-002 transgene sequence does not improve/alter the survival capacity of the GMO.

(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 GMO 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 likelihood of dissemination is lower than that of wild-type AAV. The GMO cannot replicate in the presence of a helper virus due to lack of replicase and capsid genes necessary for replication.

(d) Is the GMO in any way different from the recipient as far as pathogenicity is concerned? no

Specify Wild type AAV is non-pathogenic. If anything the vector would be even less pathogenic as there is no replication of the vector possible vs the wild type AAV which can replicate in the human host in presence of a helper virus (adenovirus).

2. Genetic stability of the genetically modified organism

As the GMO is replication incompetent Genetic Stability cannot be assessed. Even if it were replication competent, it would likely display a high degree of genetic stability due to the fact that it is a single stranded DNA virus (like wild type AAV). Genetic stability of the GMO during production was assessed and confirmed. The VTx-002 final product sequence was verified by a GMP validated Sanger sequencing method. The VTx-002 consensus sequence was found to match 100% with the theoretical sequence. Additional genome characterization was performed using next-generation sequencing, confirming genome integrity and purity (full-length genomes and >98% AAV sequences). No deviations of sequence has been observed during production of the clinical vector. AAV vectors are replication incompetent and will not replicate in vivo, therefore in vivo genetic stability is not relevant for AAV-based gene therapy vectors, and the genetic stability during production has been confirmed (described above).

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): Wild-type AAV is non-pathogenic and has not been classified under Directive 2000/54/EC of the European Parliament

and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work. AAV has no known pathogenic effects, even though the estimated seroprevalence of some common human serotypes is up to 80% (European Parliament and of the Council 2000). Consequently, AAV fulfils the definition of a Risk Group 1 biological agent according to Directive 2000/54/EC (a biological agent that is unlikely to cause human disease).

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment Enzyme linked Immunosorbent Assay (ELISA); Digital Polymerase Chain Reaction (dPCR)

(b) Techniques used to identify the GMO Enzyme linked Immunosorbent Assay (ELISA); Digital Polymerase Chain Reaction (dPCR)

F. Information relating to the release

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

To treat disease. The release will be limited to the clinical sites participating in the Phase 1/2 multicenter, open-label study to evaluate safety, tolerability, pharmacodynamics and preliminary efficacy of VTx-002 in participants with amyotrophic lateral sclerosis (ALS).

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):

This clinical trial will take place across up to 12 sites, including sites in EU, US, and UK. At least 2 sites expected in EU (Netherlands, Belgium).

(b) Size of the site (m2)

(i) actual release site (m2) n/a

(ii) wider release area (m2) n/a

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

n/a

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

n/a

4. Method and amount of release

(a) Quantities of GMOs to be released:

While dosing will be based on the patient’s cohort, vector is only detectable after injection using sensitive qPCR analysis. Thus, the amount released is considered to be low to undetectable. Up to 12 patients are foreseen in this phase 1/2 trial. All dose preparations and administration will take place in a hospital facility, which has been audited for dealing with biologic hazardous and infectious material, including storage and

waste management.

(b) Duration of the operation:

The complete administration procedure, including VTx-002 preparation, is expected to take less than 8 hours.

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

Prior to patient dosing, the GMO will be supplied directly to the investigational pharmacy at each site in line with standard recommendations for the transport of biohazardous materials. Since the GMO is considered to be of Risk group 1 and is used in a clinical trial, its usage will be restricted to this hospital facility, which has been audited for dealing with biologic hazardous and infectious material, including storage and waste management. Biosafety Level 1 measures will be implemented. All involved personnel at the site will be trained in best biosafety practices to be applied during thawing, transport to the administration room, precautions during administration and disposal of any biological waste. Such training involves, among others, wearing adapted protective clothing and gloves, the presence of a spill kit and the decontamination of waste prior to disposal as bioharzardous waste. Viral vector shedding after injection procedure will be assessed in this clinical study. This will indicate when vector shedding in bodily fluids has ceased. As VTx-002 is non-replicative, shed vector particles are unable to multiply, and thus the spread of the GMO is inherently limited and are not expected to pose a risk of transmission.

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

Not applicable. Administration of the GMO will occur only within a controlled hospital setting

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

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) N/A

(iii) Genus Homo

(iv) Species Homo Sapiens

(v) Subspecies N/A

(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)

Applicable? Yes

Specify VTx-002 is a non-replicating, recombinant AAV gene therapy vector consisting of an AAV5-based capsid. VTx-002 carries the transgene expression cassette encoding a humanized antibody fragment, flanked by AAV2 ITRs. The antibody expression is driven by a human promoter sequence, developed by the Sponsor for ubiquitous expression of the transgene. VTx-002 is an intracellularly expressed vectorized antibody (VecTab) which targets a nuclear transcriptional repressor whose dysregulation is a hallmark of ALS pathology.

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

None expected

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

None

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

(i) Order and/or higher taxon (for animals) N/A

(ii) Family name (for plants) N/A

(iii) Genus N/A

(iv) Species N/A

(v) Subspecies N/A

(vi) Strain N/A

(vii) Cultivar/Breeding line N/A

(viii) Pathovar N/A

(ix) Common name N/A

7. Likelihood of genetic exchange in vivo

(a) from the GO to other organisms in the release ecosystem None expected

(b) from other organisms to the GMO None expected

(c) likely consequences of gene transfer None expected

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.):

All clinical experience with rAAV vectors (ROCTAVIAN and Hemgenix) as both Baculovirus-derived AAV5-based gene therapy vectors used successfully in the clinic without impact on the environment, except for intentional therapeutic effect in the patient.

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

N/A

H. Information relating to monitoring

H. Information relating to monitoring

1. Methods for monitoring the GMOs qPCR

2. Methods for monitoring ecosystem effects N/A

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms N/A

4. Size of the monitoring area (m2) N/A

5. Duration of the monitoring GMO vector shedding from participants samples will be analyzed during the study until 3 consecutive negative results are obtained for all sample types or until the end of the study follow-up period.

6. Frequency of the monitoring As defined in the clinical protocol. All samples will be collected for the individual participant at multiple post-dose time points until three consecutive negative samples have been detected for the participant for all sample types.

I. Information on post release and waste treatment

I. Information on post release and waste treatment

1. Post-release treatment of the site Decontamination of the administration room by the hospital’s standard procedures will be employed after administration. Non-disposable materials, equipment and surfaces will be decontaminated according to individual institutional practices and policies.

2. Post-release treatment of the GMOs The GMO may be destroyed at the site or returned per sponsor instructions.

3(a) Type and amount of waste generated Empty/partly empty vials containing GMO residue. Materials used for the preparation and administration of the study product, e.g., extension tubing , syringes, needles, filter, gloves, gowns, and related accessories, etc.

3(b) Treatment of waste All disposable materials (e.g. gloves, masks, syringes, needles and tubing) that come into contact with the investigational product will be disposed of as biohazardous materials according to individual institutional practices and policies. In general, the materials will be disposed of in sharps containers or biohazard bags and decontaminated by incineration.

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 No specific procedures for controlling the dissemination of the GMO in the case of unexpected spread are deemed necessary. The potential for unexpected spread of the GMO in the environment is negligible as it has been engineered to be replication defective.

2. Methods for removal of the GMOs of the areas potentially affected Please refer to section I.1 and I.2

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

4. Plans for protecting human health and the enironment in the event of an undesirable effect No undesirable effects are expected. AAVs are frequently found in humans and animals, but they are not pathogenic, virulent, allergenic, or a carrier (vector) of a pathogen. During manufacturing, the GMO is analyzed to confirm that no replication competent AAV (rcAAV) are present in the final drug product. Therefore, the GMO won’t be capable of replication regardless of presence of helper virus.