SNIF: GMOB-2024-29313

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:
Ireland

Competent Authority:
Environmental Protection Agency (EPA)

Notification number:
B/IE/24/01

Acknowledgement date:
2024-08-13

A- General information

Details of notification

Details of notification
Clinical trial involving a human medicinal product containing or consisting of GMOs. The Sponsor is developing an in vivo CRISPR/Cas9-based genome editing investigational therapeutic, NTLA-3001, for the treatment of adults with Alpha-1 Antitrypsin Deficiency (AATD)-associated lung disease.
Member State of notification
Ireland
Title of the project
Phase 1/2 Multicenter, Open-label Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of NTLA-3001 in Participants with Alpha-1 Antitrypsin Deficiency (AATD)-Associated Lung Disease.
Proposed period of release
Starting date
2024-11-15
Finishing date
2030-03-01

Notifier

Name of institute or company
Intellia Therapeutics, Inc.
Email
clinicalscience@intelliatx.com
Phone number
+1 833 888 0387
Website
Not provided
Address
40 Erie Street, Cambridge, MA
Post code
02139
Country
United States

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)

Genus: Dependovirus, Species: Adeno-associated virus (AAV), serotype 8.

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

In general, DNA viruses have greater genetic stability than RNA viruses. DNA is more thermodynamically stable than RNA and DNA replication is a less error prone process than is replication of RNA. Genetic stability of the AAV Drug Product (DP) is supported by production under cGMP regulations, and verified by testing for purity, potency and identity (capsid and vector genome identity).

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

No

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 Kingdom
Notification number
Contained use

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

The potential for unintended spread within the environment is considered low. The GMO has been engineered to be replication defective, even in the presence of a helper virus, as it lacks the rep and cap genes required for rescue/packaging. The likelihood of the GMO to become persistent or invasive is therefore negligible. Furthermore, the transgene is not expected to confer any advantage in terms of survival in the environment. Given the very narrow host range, the very low probability of acquiring replication competence, and the control measures adopted by the Sponsor, the overall risks for human health and to the environment from the GMO can be considered negligible.

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)
Not applicable
(ii) Genus
Dependovirus
(iii) Species
Adeno-associated virus
(iv) Subspecies
Serotype 8 (AAV8)
(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:
boreal
atlantic
alpine
continental
macaronesian
black_sea

mediterranean
pannonian
steppic
(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 ?
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
Specific hosts are humans and non-human primates.
(b) Is the organism an animal?
No

5(a) Detection Techniques

Detection Techniques
Enzyme linked Immunosorbent Assay (ELISA); Droplet digital Polymerase Chain Reaction (ddPCR).

5(b) Identification Techniques

Identification Techniques
See section 5(a).

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 so replication in an infected host can take from 24 to 48 hrs but does not occur in the absence of an appropriate helper virus.
(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). Replication ability depends on rep and cap viral sequences. The GMO vector is an attenuated (recombinant) AAV: genes essential for DNA replication and DNA packaging into an AAV particle have been removed. 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, AAVs have the ability to form extrachromosomal concatemers that remain episomal for extended periods of time. AAV can remain infectious for at least a month at room temperature following simple desiccation or lyophilization.
(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 wild-type AAV during construction of the GMO 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

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 Sponsor is developing an in vivo CRISPR/Cas9-based genome editing investigational therapeutic, NTLA-3001, for the treatment of adults with Alpha-1 Antitrypsin Deficiency (AATD)-associated lung disease. AAV8-1 is one of two components of the therapeutic investigational gene therapy medicinal product.

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?
Yes
Yes

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

(a) Type of vector

Plasmid
Yes
Bacteriophage
No
Virus
No
Cosmid
No
Transposable element
No
Other
No
(b) Identity of the vector
Three DNA plasmids are used for the production of the GMO: a genome of interest plasmid, a rep/cap plasmid and a helper plasmid.
(c) Host range of the vector
Bacteria and mammalian cells.
(d) Presence in the vector of sequences giving a selectable or identifiable phenotype

Yes
Antibiotic resistance
Yes
Indication of which antibiotic resistance gene is inserted
Kanamycin
Other
No
(e) Constituent fragments of the vector
The GMO vector genome is a single stranded DNA with inverted terminal repeats (ITR) at each end. The non-coding ITRs flank the SERPINA1 gene without promoters and start codons.

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

(i) transformation
No
(ii) electroporation
No
(iii) macroinjection
No
(iv) microinjection
No
(v) infection
No
Other
Yes
Specify
Transfection of mammalian cells with 3 DNA vector plasmids (including rep and cap genes), resulting in production of recombinant vector particles.

6. Composition of the insert

(a) Composition of the insert

The SERPINA1 expression cassette comprises two ITRs that flank the hA1AT coding sequence. The exact composition is considered confidential.

(b) Source of each constituent part of the insert

Gene encoding SERPINA1 expression cassette: Homo sapiens; ITRs: AAV; Bovine Growth Hormone Polyadenylation Signal: Bos taurus; Simian Virus 40 Polyadenylation Signal: Macaca mulatta polyomavirus; Splice Acceptor Site: Homo sapiens

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

ITR: genome replication and capsid packaging; Therapeutic transgene: to treat or prevent disease in the recipient; Polyadenylation signal: post transcription regulatory element required for translation of the transgene; Splice Acceptor Site: required to create a mature mRNA during transcription of the therapeutic transgene from the native albumin locus.

(d) Location of the insert in the host organism

On a free plasmid
No
Integrated in the chromosome
Yes
Other
No

(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

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
(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 would only be able to replicate if the same cell was transfected by a wild-type AAV, a helper virus and the GMO at the same time.
(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

AAV is a single stranded DNA virus that demonstrates a high degree of genetic stability. Genetic stability of the GMO is supported by production under cGMP regulations, and verified by testing for purity, potency and identity (capsid and vector genome identity).

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); Droplet digital Polymerase Chain Reaction (ddPCR).
(b) Techniques used to identify the GMO
Enzyme linked Immunosorbent Assay (ELISA); Droplet digital Polymerase Chain Reaction (ddPCR).

F. Information relating to the release

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

To prevent or 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, pharmacokinetics, and pharmacodynamics of NTLA-3001 in participants with Alpha-1 Antitrypsin deficiency (AATD)-Associated lung disease.

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):

Planned participating sites are the Beaumont Hospital and the St Jamess Hospital. This clinical trial will take place across two sites. Beaumont hospital will be the principal main site and St Jamess Hospital CRF will be the satellite site for specific study visits including administration of the Investigational Product. Beaumont Hospital is not in a position to be added to the application for the administration of NTLA-3001 at present. While it has the infrastructure and the rooms available, there is a need for an upgrade to include specific equipment as well as suitable SOPs for the management of the Pharmacy that handling of NTLA-3001 requires. The team in The Royal College of Surgeons in Ireland Clinical Research Centre (RCSI-CRC) and Beaumont Hospital will work with the St. James Clinical Research Facility (CRF), who are in a position to participate as a satellite site for this trial for the administration of NTLA-3001 and the oversite and management of the patients for the treatment phase. Beaumont Hospital will remain as the lead site for the study, with Prof McElvaney as the Principal Investigator. Patients will be recruited to the study in Beaumont Hospital and will have their follow-up visits there. St. James CRF is an experienced site and has the appropriate facilities, access to the St. James Hospital and expertise for the administration of NTLA-3001 in the study, having delivered Phase 1 studies with similar products in recent times.

(b) Size of the site (m2)

(i) actual release site (m2)
Not applicable. A specific size for the site of release cannot be defined as the GMO will be administered to patients as part of a clinical trial.
(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. The GMO will be administered one-time by intravenous infusion in a hospital setting. Thus, it is not anticipated to come into contact with any recognised biotopes or protected areas.

(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:

It is expected that for a 60kg participant, administered with the high dose, 180 ml of GMO will be required. Approximately 30 participants will be enrolled globally to study intervention, of which around 5 participants in Ireland. Therefore, a total release of 900 ml of GMO is expected in Ireland.

(b) Duration of the operation:

The study duration will be approximately 162 weeks (up to 6 weeks Screening, NTLA-3001 administration on Day 1, and 156 weeks of postdose followup). The GMO will be administered via IV infusion.

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

The GMO will be supplied to St Jamess Hospital (Dublin) ensuring no long-term storage. 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.

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)
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
NTLA-3001 is a one-time administered investigational transgene insertion product for the treatment of AATD-associated lung disease. The approach being used for NTLA-3001 involves using CRISPR/Cas9 technology to site-specifically introduce a copy of the therapeutic transgene, in this case wild-type SERPINA1, into the albumin locus in the hepatocyte genome for durable, non dilutive transgene persistence.

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)
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
None expected.
(b) from other organisms to the GMO
None expected.
(c) likely consequences of gene transfer
To treat and or prevent disease.

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.):

None available.

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
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
GMO vector shedding from participants samples will be analyzed during the study through 156 weeks postdose.
6. Frequency of the monitoring
As defined in the clinical protocol. All samples will be collected until either below the lower limit of quantitation (LLOQ) in 3 consecutive samples or reaching a plateau in 3 consecutive samples.

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 hospitals 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 to the depot.
3(a) Type and amount of waste generated
Empty/partly empty vials containing GMO residue. The number of vials will vary depending on the dose cohort and the body weight of the patients enrolled. Materials used for the preparation and administration of the study product, e.g., tubing, syringes, needles, gloves, gowns, syringe, infusion bag, tubing and related accessories, etc.
3(b) Treatment of waste
All disposable materials (including but not limited to 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

Not applicable.

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 wont be capable of replication regardless of presence of helper virus.