SNIF: GMOB-2023-16976

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/23/008

Acknowledgement date:
2023-06-21

A- General information

Details of notification

Details of notification
B/NL/23/008
Member State of notification
Netherlands
Title of the project
Lentiviral or retroviral transduced human cells to prevent or treat disease
Proposed period of release
Starting date
2023-07-01
Finishing date
2033-06-30

Notifier

Name of institute or company
Princess Maxima Center for pediatric oncology
Email
f.m.bitter@prinsesmaximacentrum.nl
Phone number
+31622461744
Website
https://www.prinsesmaximacentrum.nl/nl
Address
Heidelberglaan 25 Utrecht
Post code
3584CS
Country
Netherlands

GMO characterisation

(a) Indicate whether the GMO 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

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

Human cells (macrophages and macrophage-like cells excluded) transduced with lentiviral or retroviral particles that express a non-harmful protein

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

yes

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?

No

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

An environmental impact is negligible. De viral vector used to transduce the human cells is replication incompetent by nature. The transgene sequence is not harmful. The product is administered in a hospital setting. The product will not reach the environment at large.

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
No
Bacterium
No
Fungus
No
Animal
Yes

Select from following options:

Mammal
Yes
Insect
No
Fish
No
Other animal
No
Other
No

2. Name

(i) Order and/or higher taxon (for animals)
Primates
(ii) Genus
Homo
(iii) Species
sapiens
(iv) Subspecies
Human
(v) Strain
N/A
(vi) Pathovar (biotype, ecotype, race, etc.)
N/A

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:
no
(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 ?
No
Specify
(b) Is the organism an animal?
No

5(a) Detection Techniques

Detection Techniques
not applicable

5(b) Identification Techniques

Identification Techniques
not applicable

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

No

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:
not applicable for human cells
(b) Generation time in the ecosystem where the release will take place:
not applicable for human cells
(c) Way of reproduction
Asexual
(d) Factors affecting reproduction:
not applicable for human cells

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
N/A
(b) Relevant factors affecting survivability
The survival of human cells requires a complex combination of proper-special media, temperature and CO2. The environmental conditions outside the host are substantially different and not appropriate for its survival (temperature, pH, UV, and a change in the biophysical and biochemical conditions).

10(a) Ways of dissemination

Human cells can only be transmitted between individuals through injection. No dissemination in the environment is possible due to fast inactivation.
10(b) Factors affecting dissemination
Human cells can only be transmitted between individuals through injection. No dissemination in the environment is possible due to fast inactivation.

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
No
Base substitution
No
Cell fusion
No
Other
No

2. Intended outcome of the genetic modification

Genetically modified human cells are administered to prevent or treat disease

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

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

(a) Type of vector

Plasmid
No
Bacteriophage
No
Virus
Yes
Cosmid
No
Transposable element
No
Other
No
(b) Identity of the vector
Replication deficient lentiviral (3rd or 2nd generation) SIN, or retroviral vectors
(c) Host range of the vector
Depending on pseudotype, many different human and animal cells
(d) Presence in the vector of sequences giving a selectable or identifiable phenotype
Yes
Antibiotic resistance
No
Other

Yes
Specify
transgene may be detected using standard molecular biological techniques
(e) Constituent fragments of the vector
Self-inactivating replication deficient lentiviral (derived from HIV-1) or replication deficient retroviral (derived from Murine stem cell virus (MSCV) or Moloney murine leukemia virus (MMLV) or comparable gamma-retrovirus) vector including an expression cassette for the expression of a therapeutic/preventive transgene

(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
transduction

6. Composition of the insert

(a) Composition of the insert

The transgene expression cassette maximally harbours a) one or more mammalian promoter(s) b) one or more mammalian enhancers(s) c) the therapeutic gene(s); one or more non-harmful sequence with the intention to prevent or treat disease (therapeu-tic transgene(s)) in the clinical trial subject that: i) Will, apart from the intended clinical effect, not encode a gene product with established or putative toxic, car-cinogenic, allergenic, pathogenic or immune modulating function or potential in relation to the environment. ii) will not contain sequences that contribute to the spreading of the genetic material iii) will not contain sequences that contribute to antibiotics resistance iv) will not contain sequences that affect the replication incompetence of the clinical vector v) will not contain sequences that change host range of the vector vi) will not contain sequences promoting pathogenicity or virulence of the vector vii) will not enable the formation of gene drives viii) will not result in germ line modification d) accessory genes beneficial for the expression, stability or function of the transgene that will additionally comply with the restrictions listed under 26.c.i-26.c,viii e) accessory genes beneficial for the expression, stability or function of the transgene will not contain lentiviral or retro-viral sequences f) internal ribosome entry sites that is placed between insert to be expressed and serves as an internal promoter for the downstream therapeutic transgene g) termination/polyadenylation sequence that may not be retrovirus derived h) woodchuck hepatitis virus posttranscriptional regulatory element WPRE or a deleted version of WPRE i) non-harmful human accessory sequences

(b) Source of each constituent part of the insert

see 6a

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

see 6a

(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
Yes
DNA virus
No
Bacterium
No
Fungus
No
Animal
No
Other
No

2. Complete name

(i) Order and/or higher taxon (for animals)
not applicable
(ii) Family name (for plants)
no plants
(iii) Genus
Retrovirus / Gamma retrovirus
(iv) Species
Human Immunodeficiency Virus / Murine stem cell virus, Moloney murine leukemia virus or comparable gamma-retrovirus.
(v) Subspecies

- / Oncovirinae type C (subfamily)
  (vi) Strain
  HIV-1 / -
  (vii) Cultivar/Breeding line
  not applicable
  (viii) Pathovar
  not applicable
  (ix) Common name
- / gammaretrovirus

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

yes

If yes, specify the following:

(a) to which of the following organisms?

humans
Yes
animals
No
plants
No
Other
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?

Yes
If yes, specify the following:
Yes for HIV-1: Wild type HIV is classified as group 3 organism. However, the replication-defective lentiviral vector used for transduction of human cells is not pathogenic anymore as no infectious viral particles can be produced after transduction. No for gammaretroviral vectors.

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
(b) Is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?
no
Specify
(c) Is the GMO in any way different from the recipient as far as dissemination is concerned?
no
Specify
(d) Is the GMO in any way different from the recipient as far as pathogenicity is concerned?
no
Specify

2. Genetic stability of the genetically modified organism

The therapeutic transgene is introduced into the human cells using lentiviral/retroviral gene transfer. No new viral particles can be assembled in the final host cell due to the absence in this proviral form of all the accessory proteins that confers infectivity and replicative potential. In addition, the transgene inserted in the viral vector encodes a non- hazardous inserts.

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):
No new viral particles can be assembled in the final host cell due to the absence in this proviral form of all the accessory proteins that confers infectivity and replicative potential. In addition, the transgene inserted in the viral vector encodes a non- hazardous inserts.

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment
Standard molecular biology techniques
(b) Techniques used to identify the GMO
Standard molecular biology techniques

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 in humans, no environmental benefits are 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?

No

3. Information concerning the release and the surrounding area

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

The administration/treatment will be performed in a hospital under standard hospital routines

(b) Size of the site (m2)

(i) actual release site (m2)
not relevant
(ii) wider release area (m2)
not relevant

(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:

based on the national environmental risk assessment, there are no restrictions with respect to the amount of transduced cells administered.

(b) Duration of the operation:

not defined

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

standard hospital routines are applied. In case of the application of a therapeutical product with between 1 and maximum 1*1012 residual lentiviral vector particle, In accordance with Bijlage 10, Deel D, of the Regeling ggo, the following risk minimization measures will be applied: Following administration of the medicinal product the test subject remains in the hospital for at least 16 hours to ensure that the standard hospital hygiene measures are taken; After administration of the medicinal product the infusion site will be disinfected adequately to inactivate any residing vector particles, and standard hospital hygiene measures during the care of the test subject are taken; The test subject, medical personnel and visitors should be informed about protocols and safety measures during the first 16 hours after administration of the medicinal product.

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

standard hospital conditions

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 present

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?
No

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

Applicable?
Yes
Specify
The intended result is the prevention or treatment of disease

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

Non 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, the environmental risk of the systems used is 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)
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
(b) from other organisms to the GMO:
none
(c) likely consequences of gene transfer**
not applicable

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.):

not applicable

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

none

H. Information relating to monitoring

H. Information relating to monitoring

1. Methods for monitoring the GMOs
standard molecular biology techniques
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
not defined
6. Frequency of the monitoring
not defined

I. Information on post release and waste treatment

I. Information on post release and waste treatment

1. Post-release treatment of the site
n.a.
2. Post-release treatment of the GMOs
n.a.
3(a) Type and amount of waste generated
n.a.
3(b) Treatment of waste
n.a.

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
standard hospital procedures
2. Methods for removal of the GMOs of the areas potentially affected
standard hospital procedures
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
standard hospital procedures