SNIF: GMOB-2024-30970

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:
Norway

Competent Authority:
Section for Invasive Species and International Trade

A- General information

Details of notification

Details of notification
Study YTB323
Member State of notification
NOT PROVIDED
Title of the project
CD19-directed CAR-T cell therapy (YTB323) in patients with B-cell malignancies or autoimmune diseases.
Proposed period of release
Starting date
2024-10-31
Finishing date
2034-10-31

Notifier

Name of institute or company
Novartis Pharma AG, Postfach, 4002 Basel, Switzerland
Email
Not provided
Phone number
Not provided
Website
Not provided
Address
Not provided
Post code
Not provided
Country
Not provided

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

(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?

Yes
Country
Austria
France
Germany
Spain
Italy
Netherlands

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

Yes
Country
AT
Notification number
Not provided
Country
DE
Notification number
Not provided
Country
IT
Notification number
Not provided
Country
FR

Notification number
Not provided
Country
ES
Notification number
Not provided

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
Not provided
Country
Australia
Notification number
Not provided
Country
Japan
Notification number
Not provided

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

An environmental impact is not expected as the release of YTB323 (transduced autologous T cells) is limited to patient administration in hospital settings. According to the environmental risk assessment YTB323 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
Homo sapiens
(iv) Subspecies
NA
(v) Strain
NA
(vi) Pathovar (biotype, ecotype, race, etc.)
NA

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:
notKnown
(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?
Yes
Natural habitat or usual agroecosystem
NA, Parental organism and recipient are human

5(a) Detection Techniques

Detection Techniques
Common techniques of blood cell analysis

5(b) Identification Techniques

Identification Techniques
Common techniques of blood cell analysis

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:
NA
(b) Generation time in the ecosystem where the release will take place:
NA
(c) Way of reproduction
Sexual
(d) Factors affecting reproduction:
NA

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
Not applicable for human T cells as they cannot survive outside the human body
(b) Relevant factors affecting survivability
The survival of human blood cells requires a complex combination of 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

Blood 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
The immune system of people other than the donor will eliminate the blood cells.

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)

NA

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

YTB323 is a novel, investigational, adoptive cancer immunotherapy whereby autologous T cells are genetically modified to express a transmembrane chimeric antigen receptor (CAR) to target CD19 on the cell surface of (malignant) B cells. YTB323 is also being explored in autoimmune diseases involving pathogenic B cells such as severe refractory Systemic Lupus Erythematosus (srSLE).

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
No
Bacteriophage
No
Virus
Yes
Cosmid
No
Transposable element
No
Other
No
(b) Identity of the vector
VSV-G pseudotyped replication-deficient HIV-1-derived viral vector of the 3rd generation.
(c) Host range of the vector
The viral vector is pseudotyped, since it has the Vesicular Stomatitis Virus (VSV) envelope VSV-G, which provides the capacity to transduce many different non-dividing human and animal cells.

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype
No
(e) Constituent fragments of the vector
Self-inactivating replication deficient lentiviral vector including minimal HIV-1 derived sequences required for vector packaging, reverse transcription and integration of the vector genome into the host cell genome (LTRs, packaging signal, RRE and CPPT) in addition the expression cassette for the expression of an anti-CD19 directed chimeric antigen receptor.

(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 vector sequence integrated into the CTL019 cell genome consist of minimal HIV-1 derived self-inactivating lentiviral sequences required for vector packaging, reverse transcription and integration of the vector genome into the host cell genome (LTRs, packaging signal, RRE and cPPT) in addition to the transgene expression cassette. The transgene expression cassette contains the human elongation factor 1 (EF-1) promoter controlling transgene expression, the transgene and a modified woodchuck hepatitis virus posttranscriptional regulatory element (WPRE), wherein the promoter and X-protein start codon have been mutated to prevent expression, for improved RNA translation and hence increased expression. The transgene is a chimeric antigen receptor targeted against the CD19 antigen (CAR-19). It consists of a murine anti-CD19 scFv, a human CD8 hinge and transmembrane domain, and human 4-1BB (CD137) and CD3 (T-cell receptor) intracellular signalling domains.

(b) Source of each constituent part of the insert

Lentiviral sequences from HIV; WPRE from the Woodchuck HBV virus; anti-CD19 scFV from mouse; and other parts of the CAR from human, as indicated above in (a).

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

See above.

(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
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)
NA
(ii) Family name (for plants)
NA
(iii) Genus
Retrovirus
(iv) Species
Human Immunodeficiency virus
(v) Subspecies
NA
(vi) Strain
HIV-1
(vii) Cultivar/Breeding line
NA
(viii) Pathovar
NA
(ix) Common name
NA

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?
yes
Give the relevant information specified under Annex III A, point II, (A)(11)(d) of Directive 2001/18/EC
Wild type HIV is classified as group 3 organism. However, the replication-defective lentiviral vector used for transduction of T cells is not pathogenic anymore as no infectious viral particles can be produced after transduction.

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
Not provided
(b) Is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?
no
Specify
Not provided
(c) Is the GMO in any way different from the recipient as far as dissemination is concerned?
no
Specify
Not provided
(d) Is the GMO in any way different from the recipient as far as pathogenicity is concerned?
no
Specify
Not provided

2. Genetic stability of the genetically modified organism

The chimeric antigen receptor is introduced in the T cells via lentiviral gene transfer and after integration of the SIN vector the gene modified autologous T cells are genetically stable and an integral part of the host DNA.

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):
The replication-deficient lentiviral vector genome is integrated as provirus in the T cell genome. No new viral particles can be assembled in the final host cell since the gag gene is not present. In addition, all accessory elements are absent from this viral vector. The transgenes inserted in the lentiviral vector do not code for pathogenicity factors, cytokine-coding sequences, oncogenes, antibiotic resistance genes or otherwise hazardous inserts.

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment
Post-administration monitoring of patients for persistence of YTB323 is done using qPCR of the transgene.
(b) Techniques used to identify the GMO
Identity of YTB323 is determined by qPCR in transduced cells.

F. Information relating to the release

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

Treatment of B cell malignancies and autoimmune diseases as well as neuroscience involving pathogenic B cells, in which B cells play a key role in pathogenesis through the secretion of pathogenic autoantibodies. YTB323 treatment is not expected to have any effects on the environment, at large, neither negative nor positive.

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):

Hospitals across Europe

(b) Size of the site (m2)

(i) actual release site (m2)
NA, hospital
(ii) wider release area (m2)
NA, hospital

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

NA

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

NA

4. Method and amount of release

(a) Quantities of GMOs to be released:

YTB323 is a single infusion treatment. The maximum target dose a patient might receive is 12.5 x 10E6 transduced viable T cells per dose.

(b) Duration of the operation:

The administration will take up to 60 minutes.

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

Standard Hospital Hygiene Measures.

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

Short description of average environmental conditions (weather, temperature, etc.) Hospital rooms have to fulfill hygiene conditions required for the treatment of immune- compromised patients.

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

Various clinical studies in ALL, CLL, and NHL have been carried out and are ongoing with Kymriah product which uses the same lentiviral vector. A long term follow-up study, required for patients exposed to gene therapy products, is ongoing. The GMO has already been released to the environment as part of completed or ongoing clinical trials of Kymriah product without evidence of environmental or human health impacts.

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)
NA
(iii) Genus
Homo
(iv) Species
Homo sapiens
(v) Subspecies
NA
(vi) Strain
NA
(vii) Cultivar/Breeding line
NA
(viii) Pathovar
NA
(ix) Common name
human

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

Applicable?
No

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, except the dedicated patients who receive the product. Exposure requires direct injection of YTB323. Immune-repressed individuals other than the patients will not participate in the administration of YTB323.

Persons with a functional immune system would eliminate YTB323 upon accidental injection. Simple contact exposure to blood from treated patients will not result in transmission of YTB323 as cells are quickly inactivated under environmental conditions.

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)
NA
(ii) Family name (for plants)
NA
(iii) Genus
NA
(iv) Species
NA
(v) Subspecies
NA
(vi) Strain
NA
(vii) Cultivar/Breeding line
NA
(viii) Pathovar
NA
(ix) Common name
NA

7. Likelihood of genetic exchange in vivo

(a) from the GO to other organisms in the release ecosystem
Highly unlikely
(b) from other organisms to the GMO
Highly unlikely
(c) likely consequences of gene transfer
Highly unlikely

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. No such studies have been conducted.

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
No specific GMO monitoring is proposed.
2. Methods for monitoring ecosystem effects
NA
3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
NA
4. Size of the monitoring area (m2)
NA
5. Duration of the monitoring
NA
6. Frequency of the monitoring
NA

I. Information on post release and waste treatment

I. Information on post release and waste treatment

1. Post-release treatment of the site
Standard Hospital Hygienic Procedures
2. Post-release treatment of the GMOs
None
3(a) Type and amount of waste generated
Contaminated material used for the administration of YTB323 is composed of disposables.
3(b) Treatment of waste
All disposable waste that has been in contact with the genetically modified human cells during preparation and administration will be disposed of as specific hospital waste or as waste containing GMOs.

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 spread of the GMO is expected. In case of spills decontamination with disinfectants and cleaning according to standard hospital procedures.

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

Decontamination with disinfectants and cleaning according to standard hospital procedures.

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

NA

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

NA