

SUMMARY NOTIFICATION INFORMATION FORMAT FOR PRODUCTS CONTAINING
GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS IN
ACCORDANCE WITH ARTICLE 11 OF DIRECTIVE 2001/18/EC

CTL019
Autologous genetically modified T cells, intravenous infusion
Treatment of relapsed/refractory B cell malignancies

A. General information

1. Details of notification

- (a) Member State of notification Spain
- (b) Notification number **B/ES/15/08**
- (c) Name of the product CTL019
- (d) Date of acknowledgement of notification 23/10/2015
- (e) Proposed period of release: from 01/01/2016 to 31/12/2020

2. Notifier

Novartis Pharma AG, Postfach, 4002 Basel, Switzerland

3. GMO characterisation

(a) Indicate whether the GMO is a:

- viroid (.)
- RNA virus (.)
- DNA virus (.)
- bacterium (.)
- fungus (.)
- animal
- mammals (x)
- insect (.)
- fish (.)
- other animal (.)

specify phylum, class human

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

CD4+ and CD8+ T cells transduced with a replication-deficient HIV-1 derived viral vector to express a transmembrane chimeric (murine/human) antigen receptor (CAR).

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

yes

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

Yes No

If yes, insert the country code(s) Germany, Belgium, The Netherlands, Austria, Spain, Italy, Norway, France (by different companies of the group-Novartis Pharma)

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

Yes No

If yes:

- Member State of notification DE, BE, NL, AT, ES, IT, NO, FR
(notified by different companies of the group-Novartis Pharma)
- Notification number N.A.

Please use the following country codes:

Austria AT; Belgium BE; Germany DE; Denmark DK; Spain ES; Finland FI; France FR; United Kingdom GB; Greece GR; Ireland IE; Iceland IS; Italy IT; Luxembourg LU; Netherlands NL; Norway NO; Portugal PT; Sweden SE

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

Yes No

If yes:

- Member State of notification: US, Japan, Canada, Australia (notified by different companies of the group-Novartis Pharma)
- Notification number: not applicable

7. Summary of the potential environmental impact of the release of the GMOs.
An environmental impact is not expected as the release of the CTL019 transduced autologous T cells are limited to patient administration in hospital settings. According to the environmental risk assessment CTL019 will not reach the environment at large.

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

1. Recipient or parental organism characterisation:

(a) Indicate whether the recipient or parental organism is a:

(select one only)

- viroid
- RNA virus
- DNA virus
- bacterium
- fungus
- animal
- mammals
- insect
- fish
- other animal

(specify phylum, class) human

other, specify ...

2. Name

- (i) order and/or higher taxon (for animals) Homo sapiens
- (ii) genus ...
- (iii) species ...
- (iv) subspecies ...
- (v) strain ...
- (vi) pathovar (biotype, ecotype, race, etc.) ...
- (vii) common name human

3. Geographical distribution of the organism

- (a) Indigenous to, or otherwise established in, the country where the notification is made:
Yes No Not known

- (b) Indigenous to, or otherwise established in, other EC countries:
(i) Yes , following questions not applicable to humans

If yes, indicate the type of ecosystem in which it is found:

- Atlantic ..
- Mediterranean ..
- Boreal ..
- Alpine ..
- Continental ..
- Macaronesian ..

- (ii) No
- (iii) Not known

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

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

4. Natural habitat of the organism

- (a) If the organism is a microorganism

- water
- soil, free-living
- soil in association with plant-root systems
- in association with plant leaf/stem systems
- other, specify ...

(b) If the organism is an animal: natural habitat or usual agroecosystem:
Human

5. (a) Detection techniques
Common techniques of blood cell analysis

(b) Identification techniques
Common techniques of blood cell analysis

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

Yes (x) No (.)

plants (.)

other (.)

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

Yes (.) No (x) Not known (.)

If yes:

(a) to which of the following organisms:

humans (.)

animals (.)

plants (.)

other (.)

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

The recipients cells from which the GMO is derived (autologous T-cells) are patient-specific and do not survive outside the patient from which the cells were derived. The cells are not pathogenic and do not persist or replicate in the environment or other organisms.

Patients will be tested for HIV, HBV and HCV prior to blood donation and excluded from the study if tested positive. In addition, the apheresis site is instructed to obtain additional viral serology assessments as per local guidelines. Nevertheless, patient autologous T cells should be handled as potentially containing infectious agents on the basis that pre-screening for blood borne pathogens is not exhaustive and cannot completely exclude the potential for such agents to be present.

8. Information concerning reproduction: not applicable for human T-cells

(a) Generation time in natural ecosystems:

...

(b) Generation time in the ecosystem where the release will take place:

...

(c) Way of reproduction: Sexual .. Asexual ..

(c) Factors affecting reproduction:

...

9. Survivability

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

- (i) endospores (.)
- (ii) cysts (.)
- (iii) sclerotia (.)
- (iv) asexual spores (fungi) (.)
- (v) sexual spores (funghi) (.)
- (vi) eggs (.)
- (vii) pupae (.)
- (viii) larvae (.)
- (ix) other, specify ...

(b) relevant factors affecting survivability:

The survival of human blood 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

Blood cells can only be transmitted between individuals through injection. No dissemination in the environment is possible due to fast inactivation.

(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)

..., B/././...

C. Information relating to the genetic modification

1. Type of the genetic modification

- (i) insertion of genetic material (x)
- (ii) deletion of genetic material (.)
- (iii) base substitution (.)
- (iv) cell fusion (.)
- (v) others, specify ...

2. Intended outcome of the genetic modification

CTL019 (CART-19) (tisagenlecleucel-T) 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.

3. (a) Has a vector been used in the process of modification?
Yes (x) No (.)

If no, go straight to question 5.

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

If no, go straight to question 5.

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

- (a) Type of vector

plasmid (.)
bacteriophage (.)
virus (x)
cosmid (.)
transposable element (.)
other, specify ...

- (b) Identity of the vector

Replication-deficient HIV-1-derived viral vector of the 3rd generation.

- (c) Host range of the vector

VSV-G pseudotyped and thus able to transduce many different non-dividing human and animal cells.

- (d) Presence in the vector of sequences giving a selectable or identifiable phenotype
Yes (x) No (.)

antibiotic resistance (.)
other, specify Selection of transduced cells through CAR-expression flow cytometry, that is detection of expression of the transgene, i.e., the chimeric antigen receptor targeted against the CD19 antigen (CAR-19).

Indication of which antibiotic resistance gene is inserted

...

- (e) Constituent fragments of the vector

Self-inactivating replication deficient lentiviral vector including an expression cassette for the expression of an anti-CD directed chimeric antigen receptor.

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

(i) transformation (.)
(ii) electroporation (.)
(iii) macroinjection (.)
(iv) microinjection (.)

- (v) infection
- (vi) other, specify ... transduction

5. If the answer to question B.3(a) and (b) is no, what was the method used in the process of modification?

- (i) transformation
- (ii) microinjection
- (iii) microencapsulation
- (iv) macroinjection
- (v) other, specify ...

6. Composition of the insert

(a) Composition of the insert

The transfer plasmid is a fully synthetic, HIV-1 derived self-inactivating (SIN), replication deficient vector that comprises a 5' U3 deleted Long Terminal Repeat (LTR) and a 3' U3 deleted LTR. Transcription of the genome is driven by a human cytomegalovirus (CMV) promoter fused to the 5' RU5. The 3' RU5 acts as a polyadenylation signal. A secondary polyadenylation signal (from SV40) has been inserted downstream of the 3' LTR. The vector also contains several other regulatory elements: (i) the HIV-1-derived central polypurine tract and central termination sequence (cPPT/CTS) for improved transduction efficiency, (ii) the HIV-1 rev response element (RRE) for RNA transport (this element contains the tat1, rev2 splice acceptor), (iii) the 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, and the HIV-1 packaging sequence to ensure efficient RNA packaging within vector particles. 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 α hinge and transmembrane domain, and human 4-1BB (CD137) and CD3 ζ (T-cell receptor ζ) intracellular signaling domains. Of HIV origin are the LTRs, the packaging signal and a non-functional gag sequence.

(b) Source of each constituent part of the insert

HIV, CMV, Woodchuck HBV, mouse and human, as indicated above.

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

See above

(d) Location of the insert in the host organism

- on a free plasmid
- integrated in the chromosome
- other, specify ...

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

Yes No

If yes, specify ...

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

1. Indicate whether it is a:

- viroid
- RNA virus
- DNA virus
- bacterium
- fungus
- animal
 - mammals
 - insect
 - fish
 - other animal
- (specify phylum, class) ...
- other, specify ...

2. Complete name

- (i) order and/or higher taxon (for animals) ...
- (ii) family name for plants ...
- (iii) genus Retrovirus
- (iv) species Human Immunodeficiency Virus
- (v) subspecies ...
- (vi) strain HIV-1
- (vii) cultivar/breeding line ...
- (viii) pathovar ...
- (ix) common name ...

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

Yes No Not known

If yes, specify the following: Causing AIDS

(a) to which of the following organisms:

- humans
- animals
- plants
- other ..

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

Yes No Not known

If yes, give the relevant information under Annex III A, point II(A)(11)(d):

...

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 to exposure to biological agents at work?

Yes No
If yes, specify 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.

5. Do the donor and recipient organism exchange genetic material naturally?
Yes No Not known

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?
Yes No Not known
Specify ...

(b) is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?
Yes No Unknown
Specify ...

(b) is the GMO in any way different from the recipient as far as dissemination is concerned?
Yes No Not known
Specify ...

(c) is the GMO in any way different from the recipient as far as pathogenicity is concerned?
Yes No Not known
Specify ...

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 harmful in any way (including its extracellular products), either living or dead?

Yes No Unknown

- (a) to which of the following organisms?

humans
animals

plants (.)
other ...

- (b) give the relevant information specified 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 cannot be transcribed for the lack of the plasmid that codes for the gag. In addition, the pol and 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 CTL019 will take place using qPCR for the transgene, CAR-19.

- (b) Techniques used to identify the GMO
Identity of CTL019 is determined by qPCR in transduced cells. The sequence data obtained from sequencing the integrated CTL019 (murine)-HIV-1 vector ‘from LTR to LTR’ is identical to the expected sequence as was specified by the transgene plasmid.

F. Information relating to the release

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

B cell malignancies comprise a heterogeneous group of neoplasms including a vast majority of acute lymphoblastic leukaemia (ALL), chronic lymphocytic leukaemia (CLL) and non-Hodgkin’s lymphoma (NHL). Current treatments for B cell malignancies include chemotherapy, radiation therapy, bone marrow transplantation, and peripheral blood or cord blood stem cell transplantation. Despite these treatment modalities many relapsed/refractory (r/r) patients are incurable.

Early results from ongoing clinical trials of CTL019 in r/r CLL, NHL and ALL have shown anti-tumor efficacy. It is anticipated that CTL019 may offer a therapeutic alternative for patients with relapsed/refractory B-cell malignancies who are either Stem Cell Transplantation ineligible patients or patients failing Stem Cell Transplantation, which may offer a greater durability of response than current salvage therapies. CTL019 also may have the potential to replace Stem Cell Transplantation as a therapeutic choice, expanding patient eligibility by obviating the need for matched donors along with potentially lower rates of upfront mortality and morbidity.

CTL019 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?

Yes (.) No (x)

If yes, specify ...

3. Information concerning the release and the surrounding area
 - (a) Geographical location (administrative region and where appropriate grid reference):
The Clinical Trials will take place at a number of hospitals within the Community. In Spain the clinical trials will take place in Hospital Sant Joan de Déu.
 - (b) Size of the site (m²): The administration site is a hospital room.
 - (i) actual release site (m²): ... m²
 - (ii) wider release site (m²): ... m²
 - (c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:
No environmental sites outside the hospital room will be affected. Containment measures during administration of CTL019 to the patients will exclude release of CTL019 into the environment. Personal protective equipment will be used to avoid exposure to CTL019 of the medical personnel involved in the administration of the product.
 - (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:
CTL019 is a single infusion treatment. The maximum target dose a patient might receive is 5 x 10⁸ CTL019 transduced viable T cells per dose.
 - (b) Duration of the operation:
The administration will take up to 30 minutes.
 - (c) Methods and procedures to avoid and/or minimize the spread of the GMOs beyond the site of the release
Novartis is providing a Safety Summary Sheet on safe handling directions for CTL019, measures in case of accidental spills, personal protective equipment, first aid, decontamination and disposal. These measures are in place in order to avoid any release of CTL019 into the environment.
 5. 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.
No GMO specific effects on the environment have been observed during previous clinical studies with CTL019.
- 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 organism (if applicable)

- (i) order and/or higher taxon (for animals) Human
- (ii) family name for plants ...
- (iii) genus ...
- (iv) species ...
- (v) subspecies ...
- (vi) strain ...
- (vii) cultivar/breeding line ...
- (viii) pathovar ...
- (ix) common name ...

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

The purpose of administering CTL019 drug product is the treatment of B cell malignancies. Targeting CD19 by anti-CD19 CAR expressing T-cells has been shown to be effective eliminating very advanced B cell malignancies and has the potential for a clinical benefit in patients otherwise beyond treatment.

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?

Yes (.) No (x) Not known (.)

Give details

...

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 autologous CTL019 product. Exposure requires direct injection of CTL019. Immune-repressed individuals other than the patients will not participate in the administration of CTL019. Persons with a functional immune-system would eliminate CTL019 upon accidental injection. Simple contact exposure to blood from treated patients will not result in transmission of CTL019 as CTL019 is quickly inactivated under environmental conditions.

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) ...
- (ii) family name for plants ...
- (iii) genus ...
- (iv) species ...
- (v) subspecies ...
- (vi) strain ...
- (vii) cultivar/breeding line ...
- (viii) pathovar ...
- (ix) common name ...

7. Likelihood of genetic exchange in vivo

- (a) from the GMO 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 stimulated natural environments (e.g. microcosms, etc.):
No simulations other than early clinical trials as described above have been carried out.

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)
None

H. Information relating to monitoring

1. Methods for monitoring the GMOs
Patients will continue to be followed until 15 years post-CTL019 infusion per health authority guidances. Under the long term follow-up protocol, semiannual and annual evaluations will be performed on all patients who have received a CTL019 product infusion as recommended by the FDA, EMA and other health authorities in accordance with the relevant guidances. All patients who either complete the study or prematurely discontinue post-CTL019 infusion will be automatically enrolled in this destination protocol at the time of study completion/discontinuation (separate informed consent/assent forms will be provided for this protocol). One to two times a year patients will visit the clinical site for a physical exam and medical history (including concomitant medications and adverse events) with careful attention to features possibly related to lentiviral associated events such as new malignancies, new incidence or exacerbation of a pre-existing neurologic disorder, new incidence or exacerbation of a prior rheumatologic or other autoimmune disorder, or new incidence of other hematologic disorders. In addition, labs will be drawn to evaluate routine safety endpoints, CTL019 vector persistence and replication competent lentivirus (RCL).
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
See Section H1

6. Frequency of the monitoring
See Section H1

I. Information on post-release and waste treatment

1. Post-release treatment of the site
Novartis is providing a Safety Summary Sheet on safe handling directions for CTL019, measures in case of accidental spills, personal protective equipment, first aid, decontamination and disposal. These measures are in place in order to avoid any release of CTL019 into the environment.
2. Post-release treatment of the GMOs
None
3. (a) Type and amount of waste generated
Contaminated material used for the administration of CTL019 including cryobags and infusion lines that have been in contact with CTL019.
3. (b) Treatment of waste
Inactivation as potentially infectious medical waste.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread
Novartis is providing a Safety Summary Sheet on safe handling directions for CTL019, measures in case of accidental spills, personal protective equipment, first aid, decontamination and disposal. These measures are in place in order to avoid any release of CTL019 into the environment.
2. Methods for removal of the GMO(s) of the areas potentially affected
Decontamination with disinfectants.
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 environment in the event of an undesirable effect
Not applicable other than emergency response in case of accidental injection of medical personnel, which is disinfection of injection site and follow up in case of symptoms related to immune reaction against CTL019.