ANNEX, PART 1 of COUNCIL DECISION 2002/813/EC

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

A. General information

1. Details of notification

(a) Member State of notification: Germany
(b) Notification number: B/DE/19/PEI3548
(c) Date of acknowledgement of notification: 17/09/2018
(d) Title of the project: CTL019 - Autologous genetically modified T cells, intravenous infusion. Treatment of relapsed/refractory B cell malignancies
(e) Proposed period of release: From **08/Jan/2019 until 04/Apr/2025**.

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)
Autologous T cells transduced with a replication-deficient HIV-1 derived viral vector to express a 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 (x) No (.)
If yes, insert the country code(s): All Member States (Marketing Authorisation)

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

Yes (x) No (.)

If yes:

- Member State of notification: AT, BE, DE, ES, FR, IT, NO
- Notification number: B/DE/15/PEI/2484
  B/NL/15/012
  - B/ES/15/08
  - B/ES/17/04

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 (x) No (.)

If yes: USA, Australia, Canada, Japan, Switzerland

7. Summary of the potential environmental impact of the release of the GMOs.
An environmental impact is not expected as the release of tisagenlecleucel (transduced autologous T cells) is limited to patient administration in hospital settings. According to the environmental risk assessment tisagenlecleucel 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		(x)
- 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 (x) No (.) Not known (.)

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

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

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 (.) No (X)
If yes, specify
…

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
Autologous blood leukapheresis source material is controlled for viral adventitious agents as per country specific guidance. Patients will at least be tested for HIV, HBV and HCV prior to leukapheresis donation.
…

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 ..

(d) Factors affecting reproduction:
…

9. Survivability

(a) ability to form structures enhancing survival or dormancy: not applicable for human T cells as they cannot survive outside the human body

(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 special media, temperature and CO_2. 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
Tisagenlecleucel 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-CD19 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 …

4. 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 1α (EF-1α) promoter controlling transgene expression, the transgene and a modified woodchuck hepatitis virus post-transcriptional regulatory element (WPRE), wherein the promoter and X-protein start codon have been mutated to prevent expression, for improved RNA translation and hence increased expressionThe transgene is a chimeric antigen receptor targeted against the CD19 antigen (CAR-19). It consists of a murine anti-CD19 scFv, a human CD8α hinge and transmembrane domain, and human 4-1BB (CD137) and CD3ζ (T-cell receptor ζ) intracellular signalling domains.

(b) Source of each constituent part of the insert
HIV, 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 (x)
- other, specify …

(e) Does the insert contain parts whose product or function are not known?
Yes (.) No (x)
If yes, specify …

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

1. Indicate whether it is a:

viroid (.)
RNA virus (x)
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 (x) No (.) Not known (.)
If yes, specify the following: Causing AIDS

(b) to which of the following organisms:

humans	(x)
animals	(.)
plants	(.)
other	..

(b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism
Yes (.) No x 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 (x) 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 (x) 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 (x) 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 (x) Unknown (.)
Specify …

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

(d) is the GMO in any way different from the recipient as far as pathogenicity is concerned?
Yes (.) No (x) 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 (x) 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 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 tisagenlecleucel is done using qPCR of the transgene.

(b) Techniques used to identify the GMO
Identity of tisagenlecleucel 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
Tisagenlecleucel 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):
Hospitals across the EU.

(b) Size of the site (m^2): The administration site is a hospital room.
(i) actual release site (m^2): … m^2
(ii) wider release site (m^2): … m^2

(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 tisagenlecleucel to the patients will exclude release of tisagenlecleucel into the environment. Personal protective equipment will be used to avoid exposure to tisagenlecleucel 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:
Tisagenlecleucel is a single infusion treatment. The maximum target dose a patient might receive is 6×10^8 tisagenlecleucel 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 instructions on safe handling directions for tisagenlecleucel, 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 tisagenlecleucel 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.

Various clinical studies in ALL, CLL, and NHL have been carried out and are ongoing. 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 without evidence of environmental or human health impacts.

7. Interactions of the GMO with the environment and potential impact on the environment, if significantly different from the recipient or parent organism

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	…

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

tisagenlecleucel therapy is intended to treat B cell malignancies. Targeting CD19 by anti-CD19 CAR expressing T cells has been shown to be effective in eliminating B cell malignancies and has the potential for a clinical benefit in patients.

9. Any other potentially significant interactions with other organisms in the environment
None expected.

10. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?
Yes (.) No (x) Not known
(.) Give details
…

11. 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 tisagenlecleucel. Immune-repressed individuals other than the patients will not participate in the administration of tisagenlecleucel. Persons with a functional immune- system would eliminate tisagenlecleucel upon accidental injection. Simple contact exposure to blood from treated patients will not result in transmission of tisagenlecleucel as cells are quickly inactivated under environmental conditions.

12. 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	…

13. 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

14. 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.):
None

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

G. Information relating to monitoring

1. Methods for monitoring the GMOs
No specific GMO monitoring is proposed.
Patients will continue to be followed until 15 years post-infusion. All patients who either complete the clinical studies or prematurely discontinue post-infusion will be automatically enrolled in this long-term safety follow-up protocol. All other patients treated with tisagenlecleucel will be asked to participate to a Registry.

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 (m^2)
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 information to the sites on safe handling directions.

2. Post-release treatment of the GMOs
None

3. (a) Type and amount of waste generated
Contaminated material used for the administration of tisagenlecleucel is composed of disposables.

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
No spread of the GMO is expected. In case of spills decontamination as potential infectious human material is sufficient.

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.