SNIF: GMOB-2023-17819

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:
Czech Republic

Competent Authority:
Ministry of the Environment of the Czech Republic

Notification number:
B/CZ/23/04

Acknowledgement date:
2023-07-20

A- General information

Details of notification

Details of notification
Notification about a clinical trial (EU-CT number 2022-502405-15-01) using genetically modified organisms
Member State of notification
Czechia
Title of the project
CARMAN: Early treatment intensification in patients with high risk Mantle Cell Lymphoma using CAR-T-cell treatment after an abbreviated induction therapy with Rituximab and Ibrutinib and 6 months Ibrutinib maintenance (Arm A) as compared to standard of care induction and maintenance (Arm B)
Proposed period of release
Starting date
2023-05-01
Finishing date
2025-09-30

Notifier

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GMO characterisation

(a) Indicate whether the GMO is a:

Viroid
No
RNA virus
No
DNA virus
No
Bacterium

No
Fungus
No
Animal
No
Other
Yes
Specify kingdom, phylum and class
Genetically modified human autologous T lymphocytes (animalia, chordata, mammalia, primates, Homo sapiens)

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

KTE-X19 consists of autologous human CD3+ T cells transduced ex-vivo with a replication-deficient gamma-retroviral vector (PG13 CD19-H3 Vector) to express a chimeric antigen receptor (CAR) to target CD19 molecules. The GMO is contained in the medicinal product TECARTUS (BREXUCABTAGENE AUTOLEUCEL) which has a marketing authorization in the EU (EU/1/20/1492/001).

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

The organism is genetically stable.

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

Yes
Country
France
Germany
Netherlands
Spain

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
US
Insert the notification number(s) (if exist)
IND No:16675
Country
CA
Insert the notification number(s) (if exist)
MAA No: DIN 02532719
Country
GB

Insert the notification number(s) (if exist)
MAA No: PLGB 11972/0045
Country
CH
Insert the notification number(s) (if exist)
MAA No: 67884

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

An environmental impact is not expected as the release of the KTE-X19 transduced autologous T-cells is limited to patient administration in hospital settings. KTE-X19 will not reach the environment at large. The overall risk of KTE-X19 for people and the environment can be concluded to be 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
No
Bacterium
No
Fungus
No
Animal
No
Other
Yes
Specify kingdom, phylum and class
human autologous T lymphocytes (animalia, chordata, vertebrata, mammalia, primates, human)

2. Name

(i) Order and/or higher taxon (for animals)
Homo sapiens (primates)
(ii) Genus
Homo
(iii) Species
Homo sapiens
(iv) Subspecies
not applicable
(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:
mediterranean
boreal
alpine
continental

pannonian
steppic
(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
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:
Not applicable for transduced human T cells.
(b) Generation time in the ecosystem where the release will take place:
Not applicable for transduced human T cells.
(c) Way of reproduction
Asexual
(d) Factors affecting reproduction:
Not applicable for transduced human T 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
Not applicable for transduced human T cells.
(b) Relevant factors affecting survivability
The survival of human T cells requires a complex combination of special media, temperature and CO2. The environmental conditions outside the host (body) are substantially different and will not support the cells survival (temperature, pH, UV and a change in the biophysical and biochemical conditions).

10(a) Ways of dissemination

Human T cells can only be transmitted between individuals through injection. No dissemination in the environment is possible due to fast inactivation and lack of a natural entry route into the body.
10(b) Factors affecting dissemination
The immune system of people other than the donor will eliminate the T cell product (the patient-specific genetically modified T 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)

None

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

KTE-X19 is an investigational, adoptive cancer immunotherapy whereby autologous T cells are genetically modified to express an anti-CD19 transmembrane CAR that targets CD19 on the cell surface of malignant B cells. The CAR-modified T cell is activated following engagement with the CD19 target, resulting in elimination of the CD19 malignant cell.

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 gamma-retroviral vector: murine stem cell virus-based splice-gag vector (MSGV1) termed PG13-CD19-H3 Vector.
(c) Host range of the vector
The vector used is a hybrid retroviral vector consisting of the gag-pol accessory proteins from the Moloney murine leukemia virus (MoMLV) and the envelope from the gibbon ape leukemia virus (GALV), both

contained and produced in the mouse cell line PG13. The backbone containing the transgene is MSGV1, that utilizes the long terminal repeats (LTR) from the murine stem cell virus (MSCV) and an extended gag region and splice site to improve retroviral titer and expression of the transgene across different cell types. This backbone is compatible with the MoMLV retroviral accessory proteins. The PG13-CD19-H3 Vector produced in the PG13 cell line has a broad host range including rat, hamster, bovine, cat, dog, monkey and human cells .

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype

Yes

Antibiotic resistance

No

Other

Yes

Specify

The vector encodes the anti-CD19 CAR which is expressed on the surface of transduced T-cells. Cell surface expression of the CAR can be detected by flow cytometric analysis of the transduced T-cells, thereby providing an identifiable phenotype.

(e) Constituent fragments of the vector

The backbone containing the CAR sequence is MSGV1, that utilizes the long terminal repeats (LTR) from the MSCV and an extended gag region and splice site to improve retroviral titer and expression of the transgene across different cell types. Only the LTRs and the sequences contained in between are integrated in the genome of the transduced T cells as provirus. This provirus therefore, contains a 5LTR serving as promoter, a partial gag sequence and packaging signal, a CAR sequence and a 3LTR.

(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 PG13-CD19-H3 Vector encodes the anti-CD19 CAR. The process of retroviral-mediated transduction serves to integrate the CAR gene into the T cell genome. The transfer plasmid MSGV1-FMC63-CD28z is an engineered construct that was used to generate an expression cell line that constitutively produces the PG13-CD19-H3 Vector. It comprises 5 and 3 LTRs flanking a partial gag sequence, a retroviral packaging signal and the DNA sequence encoding the anti-CD19 CAR. The anti-CD19 CAR constituent consists of the following domains linked as a single chimeric molecule: A target-specific binding domain consisting of an

antibody-derived single-chain variable fragment (scFv) specific for the target antigen CD19 expressed on the surface of normal and malignant B cells; the transmembrane and hinge domains of human CD28, and the human T-cell derived activating domains CD3-zeta and CD28.

(b) Source of each constituent part of the insert

The CAR construct utilised to produce KTE-X19 has been designed, optimised and initially tested at the Surgery Branch of the NCI. The scFv fragment was derived from the variable region of the anti-CD19 monoclonal antibody FMC63 which is murine in origin. . The remainder of the CAR sequences, namely the hinge and transmembrane domains, CD3-zeta and CD28 signaling domains, are all of human origin, having been cloned from human T cells. The signaling domain of the CD3-zeta chain is of human origin and is essential for mediating T cell activation. The cytoplasmic domain of the CD28 costimulatory molecule is also included, since murine models and clinical studies have demonstrated the importance of CD28-mediated co-stimulation for optimal survival, persistence and anti-tumour activity of anti-CD19 CAR T cells . The CD3-zeta chain and CD28 fragments were cloned from human T cells into a contiguous chimeric single chain construct, and inserted in the MSGV1 plasmid.

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

Please refer to 6.a. (Composition of the insert) and 6.b. (Source of each constituent part of the insert). - As per 4.e. (Constituent fragments of the vector) the retroviral integrase mediates the insertion of the retro-transcribed viral genome into the host genome via its interaction with the two LTRs, resulting in the integration of both LTRs along with all the nucleotide sequences found in between them, including the CAR. One of the LTRs serves as the promoter once the DNA is fully incorporated in the host genome, driving the expression of the CAR. - Target Binding Domain: At one end of the CAR is a target binding domain of an antibody that is specific for the target antigen CD19 present on the surface of normal and malignant B cells. This domain extends out of the engineered T cell into the extracellular space, where it can recognise target antigens. The target binding domain consists of a single-chain variable fragment, or scFv, derived from an antibody comprising variable domains of heavy and light chains joined by a short linker. This allows the expression of the CAR as a single-chain protein. - Transmembrane Domain and Hinge: This middle portion of the CAR links the scFv target binding domain to the activating elements inside the cell. This transmembrane domain anchors the CAR in the cells membrane. In addition, the transmembrane domain may also interact with other transmembrane proteins that enhance CAR function. In the extracellular region of the CAR, directly adjacent to the transmembrane domain, lies a hinge domain. This region of the CAR provides structural flexibility to facilitate optimal binding of the CARs scFv target binding domain with the target antigen on the cancer cells surface. - Activating Domains: Located within the T cells interior are two regions of the CAR responsible for activating the T cell upon binding to the target cell. The CD3-zeta element delivers essential primary signal within the T cell, and the CD28 element delivers an additional, co-stimulatory signal that promotes T cell survival, persistence and anti-tumor activity. Together, these signals trigger T cell activation, resulting in CAR T cell proliferation and direct killing of CD19-expressing normal and malignant cells. In addition, T cell activation stimulates the local secretion of cytokines and other molecules that can recruit and activate additional anti-tumour immune cells.

(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)
Orthoretrovirinae; (subfamily Oncovirinae)
(ii) Family name (for plants)
not applicable
(iii) Genus
Gammaretrovirus
(iv) Species
Murine stem cell virus
(v) Subspecies
Oncovirinae type C (subfamily)
(vi) Strain
not applicable
(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?

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?

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 CAR is introduced in the T cells via retroviral vector gene transfer. After integration, the gene modified autologous T cells are genetically stable and form 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 retroviral vector genome is integrated as provirus in the T cell genome. 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 to the retrovirus. In addition, the transgene inserted in the retroviral vector do not code for pathogenicity factors, cytokine-coding sequences, oncogenes, antibiotic resistance genes, or other hazardous inserts.

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment
CAR expression on transduced T cells can be detected using flow cytometry.
(b) Techniques used to identify the GMO
The GMO can be identified using flow cytometry. Integrated copies of the retroviral vector can be identified in T cells by qPCR.

F. Information relating to the release

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

As most advanced cancers eventually become refractory to conventional therapies, new treatment modalities are needed. Immunotherapy, which is based on the enhancement of an immune response against the tumour, is a promising approach to treating many cancer types. T cells play an important role in destroying diseased cells throughout the body. Studies with immune checkpoint inhibitors and tumour infiltrating lymphocytes have demonstrated the potential of T cells to treat cancer. T cells need to possess the appropriate specificity for the tumour, be present in sufficient numbers, and have the ability to overcome any local immunosuppressive factors to be effective. CAR-engineered T cells are a promising approach for cancer therapy. Engineered Autologous Cell Therapy is a process by which a patients own T cells are collected and subsequently genetically altered to recognise and target antigens expressed on the cell surface of specific malignancies. The ability to genetically engineer human T cells and use them to mediate cancer regression in patients has been demonstrated in a number of studies and has opened possibilities for the treatment of patients with a wide variety of cancer types including B cell malignancies expressing the CD19 antigen. Several antiCD19 chimeric antigen receptor (CAR) T-cell therapies (axicabtagene ciloleucel (Yescarta), brexucabtagene autoleucel (Tecartus, tisagenlecleucel (Kymriah), and lisocabtagene maraleucel (Breyanzi)) are approved in the EU. Treatment with KTE-X19 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):

Each patients respective leukapheresis will be processed for T cell enrichment and transduced using the PG13-CD19-H3 Vector encoding the anti-CD19 CAR gene (which constitutes a GMO). These steps and the entire manufacture of the product will take place at Kite Pharma facilities located either in the United States of America or Hoofddorp, Netherlands. In the case of manufacture outside of the EU (for example in the USA) the finished KTE-X19 T cell product, is shipped back to Kite Pharma EU B.V., located at Hoofddorp, The Netherlands, which upon release by a qualified person, acts as the release site across the countries in Europe. The apheresis, infusion of KTE-X19, and subsequent follow-up will occur at site selected for conduct of the clinical trial.

(b) Size of the site (m2)

(i) actual release site (m2)
Not applicable.
(ii) wider release area (m2)
Not applicable.

(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 KTE-X19 to the patients will exclude release of KTE-X19 into the environment. Personal protective equipment will be used to avoid exposure to KTE-X19 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:

KTE-X19 is a single infusion treatment. The KTE-X19 drug product is formulated to provide a target dose of 0.5 x 106 to 2.0 x 106 CAR-positive T cells/kg subject body weight.

(b) Duration of the operation:

The complete administration procedure including preparation of the infusion system is expected to take less than 24 hours.

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

Kite Pharma is supplying an Investigational Product Manual which includes instructions for safe use, handling and disposal of KTE-X19 and materials. All involved personnel on the site will be trained in best practices to be applied during administration and disposal of any biological product. Disposal of waste will be according to institutional biosafety procedures for handling and disposal of blood product.

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

Hospital treatment rooms have to fulfil hygiene conditions required for the treatment of immune-compromised patients. The investigational medicinal product, KTE-X19, is stored in vapour phase of liquid nitrogen at -150C until administration.

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

Not applicable.

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
The purpose of administering KTE-X19 final product is for the treatment of B-cell malignancies. Targeting CD19 tumor cells by anti-CD19 CAR expressing T cells has been shown to be effective in eliminating advanced B-cell malignancies and has the potential for a clinical benefit in patients otherwise beyond treatment. If the modified T lymphocytes are accidentally transferred to another human, the T lymphocytes will most likely be recognised as non-self by the immune system and be destroyed.

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

None expected. Human T cells cannot survive outside the human body or in other organisms. Cross-contamination with other species is highly unlikely.

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 autologous KTE-X19 product. Exposure requires direct infusion of KTE-X19. Immune-suppressed individuals other than the patients will not participate in the administration of KTE-X19. Persons with a functional immune system would quickly eliminate KTE-X19 upon accidental injection. Simple contact exposure to blood from treated patients will not result in transmission of KTE-X19 as KTE-X19 is quickly inactivated under environmental conditions. There are no known mechanisms to enable shedding of PG13-CD19-H3 Vector from KTE-X19. PG13-CD19-H3 Vector is replication incompetent and not produced in human T cells, and human T cells do not contain the required viral elements to mobilize PG13-CD19-H3 Vector. Retroviral particles that have not entered and transduced the T cells are removed during the manufacturing process and have a short half-life under the cultured conditions. Retroviral vectors are unstable at physiological temperatures, with a half-life at 37C ranging from about 2-4 hours. Based on extensive testing of the licensure enabling clinical trials which led to Kite Pharmas commercial products (axicabtagene ciloleucel and brexucabtagene autoleucel) RCR is performed at the viral vector stage only as no RCR was ever detected in either any clinical finished product or any viral vector lots.

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:
Since human and murine retroviruses differ, it is highly unlikely that recombination with endogenous retroviruses will occur in T cells. In addition, T cells are largely unable to produce infectious virions. Furthermore, T cells cannot survive outside of the human body. Even if wild type retroviruses were present in the environment, recombination with the gamma-retroviral vector encoding the CAR used to modify the patients T cells ex vivo is extremely unlikely, since viable recombination would be most likely restricted to wild type Moloney Murine Leukaemia Virus (MoMLV), which can only infect mouse cells. Recombination with other retroviral species capable of infecting human T cells is unlikely

due to poor homology between their genomes, and in any case the CAR is unlikely to confer any selective advantage to the hypothetical recombinant.
(b) from other organisms to the GMO:
None.
(c) likely consequences of gene transfer**
Refer to G.7(a). The consequence of gene transfer is the integration in the genome of the T lymphocytes of a 5LTR serving as promoter, a partial gag sequence and packaging signal, a CAR sequence and a 3LTR. The anti-CD19 CAR will be expressed and displayed on the cell surface. Integration is the desired effect of retroviral-mediated gene transfer. However, it has been considered to carry a potential risk of insertional mutagenesis, which can result in dysregulated gene expression and subsequent malignant transformation. While the risk of insertional mutagenesis is a known possibility, this has only been observed in the setting of infants treated for X-linked SCID (severe combined immunodeficiency) using retroviral vector-mediated gene transfer into CD34+ bone marrow cells. In the case of retroviral vector-mediated gene transfer into mature T cells, there has been no evidence of insertional mutagenesis and long-term toxicities in multiple clinical trials with genetically-engineered T cell products. While Kite believes the risk of insertional mutagenesis is extremely low, patients in the KTE-X19 clinical trials receiving gene transduced cells are being monitored for long-term gene therapy related adverse events.

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.):

No simulations other than early clinical trials 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

H. Information relating to monitoring

1. Methods for monitoring the GMOs
Since the GMO KTE-X19 is contained in the medicinal product TECARTUS (BREXUCABTAGENE AUTOLEUCEL) which has a marketing authorization in the EU (EU/1/20/1492/001) and since TECARTUS (BREXUCABTAGENE AUTOLEUCEL) is applied according to the marketing authorization in humans with mantlecell lymphoma with the only differece that the patients in this clnical trial should not be pretreated, no special monitoring of the GMO is planed for this trial.
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 applicable.
6. Frequency of the monitoring
Not applicable.

I. Information on post release and waste treatment

I. Information on post release and waste treatment

1. Post-release treatment of the site
All working surfaces that came into contact with the GMO will be disinfected according to hospital/facility hygiene procedures for example a 70% ethanol solution. The hospital room will be cleaned according the institutional biosafety procedures for hospital room cleaning.
2. Post-release treatment of the GMOs
None.
3(a) Type and amount of waste generated
Empty bags and the used delivery system components (e.g., guide tube, cannula, injection needles and syringes), gauzes, personal protective equipment (e.g. gloves etc) and components used for collecting body fluids samples after administration.
3(b) Treatment of waste
Sharps such as needles will be disposed of in adequate sharp containers and incinerated. Disposables such as syringes, tubing, catheters and surgery waste (gloves, compresses) will be treated as and disposed of as biological waste according to the institutional biosafety procedures. All the surgical materials (surgery tools, linens) will be collected and autoclaved before washing or will be treated as and disposed of as biological waste. All non-disposable surgical equipment will be cleaned using a chemical disinfectant with proven virucidal activity (e.g. hypochlorite solution. 70% ethanol) and subsequently treated according to standard practice of the institution.

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

There is no risk of environmental health hazard. KTE-X19 for intravenous infusion will be prepared for administration. In case of spillage, the affected area, lineated with absorbing material, will be decontaminated using appropriate disinfectants. A spill kit will be available at all times during the administration procedure. Details are given in the Investigational Product Manual, describing the handling of the IMP, storage, and the administration procedures that will be handed over to the sites during the site initiation visit (prior to starting the study). In case of accidental exposure, the following information should be made known: Since any PG13-CD19-H3 Vector that has not integrated into the patients T cells is cleared during the manufacturing process, it is considered that neither PG13-CD19-H3 Vector used to modify the patients T cells, nor the KTE-X19 drug product itself could be inhaled as an aerosol. In case of a spill incident, washing of the contaminated skin and removal of contaminated clothes should be performed. These measures will limit exposure of KTE-X19 to unintended persons. All healthcare professionals involved in the administration will adhere to safe practices to avoid any release of the product into the environment. Work surfaces and material potentially in contact with KTE-X19 will be decontaminated according to hospital/facility hygiene procedures. In case of spillage, a spillage kit containing absorbing lining and an adequate disinfectant will be available during receipt and administration of the product. KTE-X19 is primarily composed of T cells that are too large to be absorbed percutaneously. Considering the size of the PG13-CD19-H3 Vector protein capsid (80 nm 100 nm) and weight (env encodes >70,000 Da protein) no percutaneous absorption is expected.

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

As per the GMO guidelines and the local hospital processes.

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

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 KTE-X19.