PART 1 (COUNCIL DECISION 2002/813/EC)

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

In order to tick one or several possibilities, please use crosses (meaning x or X) into the space provided as (.)

A. General information

1. Details of notification

(a) **Member State of notification** The Netherlands
(b) **Notification number** To Be Determined
(c) **Date of acknowledgement of notification** ../../….
(d) Title of the project
Testing the safety and efficacy of KITE-585 (referred to hereafter as KITE-585 or as 'the genetically modified organism [GMO]'), an autologous cellular immunotherapy composed of a patient's own T cells engineered to express anti-B-cell maturation antigen (BCMA) chimeric antigen receptors (CARs), in patients with hematologic malignancies in which BCMA is expressed on tumor cells.

(e) **Proposed period of release** 01 Jan 2019 until 01 Jan 2049

2. **Notifier**

Name of institution or company: Universitair Medisch Centrum Utrecht

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 T cells

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

Human T cells transduced with a replication-deficient lentiviral delivery system (293FT-K585 Vector) to express a fully human, anti-B-cell maturation antigen (BCMA) chimeric 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) **NL, DE, FR, and GB**.

5. Has the same GMO been notified for release elsewhere in the Community by the same notifier?
Yes (.) No **(X)**
If yes:
- Member State of notification …
- Notification number **Not applicable (NA)**

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 IND No.:** **17619**
- Member State of notification **NA**
- Notification number **NA**

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

An environmental impact is not expected as the release of the KITE-585-transduced autologous T cells is limited to patient administration in hospital settings. According to the environmental risk assessment, KITE-585 will not reach the environment at large. The overall risk of KITE-585 for people and the environment is considered negligible.

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 T cells

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**)

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

Atlantic	**X**
Mediteranean	**X**
Boreal	**X**
Alpine	**X**
Continental	**X**
Macaronesian	**X**

(ii) No (.)
(iii) Not known (.)

(c) Is it frequently used in the country where the notification is made?

Yes (**X**) No (.)

(d) Is it frequently kept in the country where the notification is made?

Yes (**X**) 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:**
Not applicable

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	**NA**
animals	**NA**
plants	**NA**
other	**NA**

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

The GMO is derived from autologous T cells isolated from the peripheral blood of patients. The production of both the replication-deficient lentiviral vector and KITE-585 (GMO), takes place in the USA, outside of the EU. Only the final product (KITE-585) that contains the engineered (genetically modified) anti-BCMA CAR T cells enters the EU. The genetically modified autologous T cells cannot survive outside of the patient from which the cells

were derived. The cells are not pathogenic and do not persist or replicate in the environment or in other organisms.

Patients will be tested for HIV, HBV and HCV prior to blood donation and excluded from the clinical trial 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:**
NA

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

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

(d) **Factors affecting reproduction:** NA

9. **Survivability**

(a) **ability to form structures enhancing survival or dormancy:** Not applicable for human T cells.

(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 T cells requires a complex combination of special media, temperature and CO_2. 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.

(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**

(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**

The anti-BCMA CAR includes the following genetic elements; an scFv fused to the hinge, transmembrane, and intracellular CD28 co-stimulatory domains, and the CD3ζ signaling domain. Upon antigen stimulation, the CAR will provide signals required for T-cell activation, which will lead to the elimination of BCMA-positive cells within the host.

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**

A self-inactivating (SIN) human immunodeficiency virus (HIV)-1-based lentiviral vector (LVV) encoding the CAR transgene, termed the 293FT-K585 Vector.

(c) **Host range of the vector**

The LVV delivery system has been altered to use a viral envelope protein from VSV-G, rather than the HIV-1 envelope protein. VSV-G confers a broad host cell range, with ability to transduce nondividing cells as diverse as HeLa cells, rat fibroblasts, and terminally differentiated neurons (Naldini et al, 1996).

It should be noted that free lentiviral particles are removed during the manufacturing process and RCL has not been observed in clinical use of LVVs (Holzinger et al, 2016; Naldini et al, 2016; Cornetta et al, 2018).

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

Yes (**X**) No (.)

antibiotic resistance (.)
other, specify The GMO contains an identifiable phenotype. Specifically, the transgene insert encodes the anti-BCMA CAR which is expressed at the membrane surface of transduced T cells. Cell surface expression of the CAR can be detected by flow cytometry.

Indication of which antibiotic resistance gene is inserted
NA

(e) **Constituent fragments of the vector**

The HIV-1-based lentiviral provirus include the following elements:

- A modified 5' long terminal repeat (LTR) with a deleted U3 element
- A packaging sequence (psi) contained within a truncated gag sequence (gag')
- The HIV-1 rev response element (RRE)
- A central polypurine tract (cPPT)
- A unique marker sequence to identify vector-transduced cells (c-frag)
- A murine stem cell virus (MSCV) promoter to drive the expression of the transgene within the target T cell
- The CAR transgene composed of 1) a novel, fully-human scFv, 2) a truncated CD28 spacer which comprises the hinge, transmembrane and cytoplasmic domains, 3) a CD28 costimulatory domain, and 4) the cytoplasmic T-cell activation domain of human CD3ζ
- A Woodchuck post-transcriptional regulatory element (WPRE)
- A truncated 3' LTR (3'-SIN LTR) containing a deletion of the U3 region to prevent mobilization of the vector

(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?** NA

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

6. **Composition of the insert**

(a) Composition of the insert

The components of the vector used to transduce human T cells with the insert are described in (C) 4. (e), Constituent fragments of the vector, above. The genetic sequences inserted into the T cells, ie, the provirus, consist of the following elements: a 5' LTR, a psi packaging sequence, an RRE, cPPT, a c-frag unique marker sequence, an MSCV promotor, the CAR transgene, a WPRE, and a 3' LTR (Table 1).

Table 1. Elements of the Provirus Incorporated to the GMO

Element	Description (and origin, where applicable)
5' LTR	Replication defective 5' long terminal region with the U3 region deleted for safety.
Packaging sequence (psi) and truncated gag sequence (gag')	Psi is an RNA structural feature required for incorporation of the viral genome within particles, ie, packaging.
RRE	Sequence to which the Rev protein binds and exports transcribed viral RNA from the nucleus into the cytoplasm of the packaging cells
cPPT	Promotes the transportation of the viral genome into the nucleus of non-dividing cells
Unique marker sequence (c-frag)	Allows identification of vector-transduced cells
MSCV promoter	Derived from MoMLV LTR, drives expression of CAR
Open reading frame	CAR transgene, recognizes and binds tightly to the BCMA antigen on MM cells, targeting these cells for killing by the engineered CAR T cells
WPRE	Sequence derived from Woodchuck hepatitis virus improves stability and expression of the CAR transgene, while minimizing read-through of the promoter
3'-SIN LTR	Required for reverse transcription of the viral genome, with deletion of U3 region to render the virus replication-incompetent

Abbreviations: CAR, chimeric antigen receptor; cPPT, central polypurine tract; gag', truncated *gag* sequence; LTR, long terminal repeat; MSCV, murine stem cell virus; RNA, ribonucleic acid; RRE, rev response element; SIN, self-inactivating; WPRE, woodchuck post-transcriptional regulatory element.

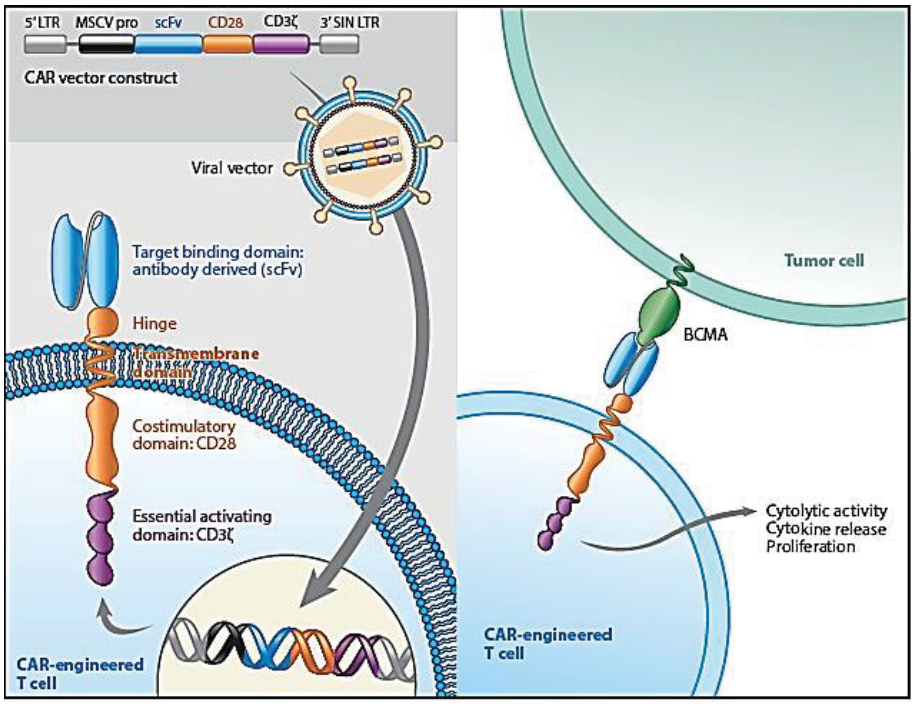
The CAR transgene is composed of the following elements, listed in order with their function in the insert noted below (Table 2):

Table 2. Elements of the CAR Transgene

Element	Description
N-terminal signal peptide from human CD8α	Directs the CAR transgene to the surface of T cells
scFv (anti-BCMA antigen recognition domain)	Derived from human anti-human BCMA monoclonal antibody RD-1; uses an 18-residue linker (Whitlow et al, 1993) to join the heavy and light chain variable domains
Human CD28 hinge, transmembrane, and intracellular signaling domains	CD28 is a T-cell specific cell surface glycoprotein
Human CD3ζ	T-cell receptor (TCR)-associated cytoplasmic activation domain

A CAR is a fusion protein consisting of an antibody-derived single-chain variable fragment (scFv) that recognizes a particular extracellular antigen, combined with T-cell activation domains located on the intracellular portion of the molecule (Holzinger et al, 2016). Engagement of the CAR with its target antigen induces T-cell activation, expansion, production of cytokines, and killing of target-expressing cells, in this case BCMA-expressing tumor cells. A schematic of this mechanism is shown in Figure 1.

Figure 1. KITE-585 Construct and Mechanism of Action



Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CD28, cluster of differentiation 28; CD3ζ, cluster of differentiation 3 δ ; LTR, long terminal repeat; MSCV pro, murine stem cell virus promoter; scFv, single-chain variable fragment; SIN, self-inactivating.

(b) Source of each constituent part of the insert

All sequences in the CAR transgene are human in origin.

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

Please refer to (C) 6. (a) Composition of the insert, above, for the function of each constituent part of the CAR.

(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**) - HIV lentiviral backbone (not in the final product)
DNA virus (.)
bacterium (.)
fungus (.)
animal
- mammals (**X**) – human CAR transgene
- 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 **Lentivirus -**
(iv) species

- **Human Immunodeficiency Virus 1 (HIV-1)**
- **Woodchuck hepatitis virus (WPRE)**

- **Gamma-retrovirus (MSCV promoter)**
- **Human (the CAR transgene)**

(v)	subspecies	NA
(vi)	strain	**HIV-1 Strain HXB2**
(vii)	cultivar/breeding line	NA
(viii)	pathovar	NA
(ix)	common name	**Lentivirus**

3. **Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?**
Yes (.) No (**X**) Not known (.)
If yes, specify the following:

(b) 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 (**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 …

5. Do the donor and recipient organism exchange genetic material naturally?
Yes (**X**) 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 (**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 CAR is introduced in the T cells via lentiviral vector gene transfer. After integration, the gene-modified autologous T cells are genetically stable. Stable presence of the insert can be verified by testing for surface expression of the CAR by flow cytometry. Additional details are provided in response to C 4 (e) above.

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 **NA**

(b) give the relevant information specified under Annex III A, point II(A)(11)(d) and II(C)(2)(i)

The vector is self-inactivating because of deletions in the U3 region of both the 5' and 3' LTRs, such that the ability to produce viral RNA from the viral LTR promoter is removed; thus, elements necessary for generating replication-competent viruses are eliminated.

Together, the absence of the HIV-1 accessory genes, coupled with removal of transcriptional elements in the 5' and 3' LTR render the vector system replication-incompetent. Further, the *gag/pol*, *env*, and *rev* sequences are not encoded by the LVV, referred to as 293FT-K585 Vector. Similarly, the packaging and structural genes are not encoded by the LVV and are therefore not transferred to the target cells. Consequently, no viral proteins will be made by the transduced cells and therefore new vector particles cannot be formed. In contrast to wild-type HIV-1,

the provirus encoded by the 293FT-K585 Vector has none of the viral machinery required for replication and generation of viral particles, once the provirus has integrated into the final host cell.

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment

KITE-585 comprises human T cells, which cannot survive outside the human body. In patients, 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 lentiviral 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)

The CAR T cell therapy will not be released into the environment. Rather, engineered autologous cell therapy is a process by which a subject's own T cells are collected and subsequently genetically engineered with a T-cell receptor or a CAR specific for a target antigen expressed on the cell surface of specific malignancies (Johnson et al, 2006; Kochenderfer and Rosenberg 2013; Robbins et al, 2015). These engineered CAR T cells are then reintroduced to the same patient. These engineered T-cell products represent a promising approach for cancer therapy (Holzinger et al, 2016). The cells cannot survive outside the body of the patient, and cannot survive in other individuals.

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):

Apheresis will take place at: Universitair Medisch Centrum Utrecht
Heidelberglaan 100, B02.226
3584 CX Utrecht

The patients' T cells will be harvested by leukapheresis at the clinical site and transported to Lonza Netherlands BV for initial processing. Manufacturing of final product will proceed at Kite, a Gilead Company; hereafter referred to as 'Kite') located in California, USA. The T cells are genetically modified at the clinical manufacturing site in compliance with current Good Manufacturing Practices.

Once KITE-585 (the GMO, consisting of autologous T cells that have been transduced ex vivo) is manufactured it will be cryopreserved, and transported in a liquid nitrogen dry shipper to Kite Pharma EU B.V., where the European qualified person (EU QP) will release the product. The product will then be transported to the clinical site according to good distribution practice (GDP).

The apheresis, infusion of KITE-585 and subsequent follow-up will occur at Universitair Medisch Centrum Utrecht NCI for studies targeting BCMA-expressing tumors. The lead investigator and the site address is as follows:

Multiple Myeloma and potentially other BCMA-expressing tumors:

Dr. Monique Minnema

Department of Hematology

Universitair Medisch Centrum Utrecht
Heidelberglaan 100, B02.226
3584 CX Utrecht

(b) Size of the site (m^2): NA
(i) actual release site (m^2): NA
(ii) wider release site (m^2): NA

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

No environmental sites will be affected. Containment measures during administration of KITE-585 to the patients will exclude release of KITE-585 into the environment. Standard personal protective equipment and sterile/aseptic precautions will be used to avoid exposure to blood and fluids of the medical personnel involved in the administration of KITE-585. KITE-585 is not capable of survival outside the human body, and would be destroyed by the immune system in a recipient other than the patient (Welsh et al, 1975; Welsh et al, 1976).

(c) **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:

KITE-585 is an intravenous infusion treatment. The KITE-585 drug product is formulated to provide a target dose of no more than 1 x 10^9 total CAR T cells.

(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 will supply an Investigational Product Manual which includes instructions for safe use, handling and disposal of KITE-585 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 the GMO guidelines and UN 3291 specific hospital waste.

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, KITE-585, is stored in vapor phase of liquid nitrogen at ≤-150°C 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.

Early results from a first-in-human clinical study of KITE-585 have demonstrated an acceptable safety profile for the initial dose cohort, and early clinical efficacy results are promising (NCT 03318861).

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 GMO is engineered to express a CAR, ie, a fusion protein consisting of an antibody-derived single chain variable region (scFv) that recognizes a particular extracellular antigen, combined with T-cell activation domains located on the intracellular portion of the molecule. The mechanism of action is given in (C) 6. (a) Composition of the insert, above. Gene and protein expression profiling has shown that BCMA is broadly expressed in certain hematologic cancers, such as MM (Tai and Anderson 2015; Hudecek and Einsele 2016), and is implicated in diffuse large B cell lymphoma (DLBCL), Hodgkin lymphoma (HL), plasmablastic lymphoma, Burkitt's lymphoma and potentially many other B-cell malignancies (Schwaller et al, 2007; Schwaller et al, 2007; Khattar et al, 2017). Its limited normal tissue distribution combined with its broad expression in most patients with MM and other potentially other hematologic malignancies makes BCMA a target to selectively kill tumor cells with KITE-585.

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 patients who receive the autologous KITE-585 product. Exposure requires direct infusion of KITE-585. Immune-suppressed individuals other than the patients will not participate in the administration of KITE-585. Persons with a functional immune system would quickly eliminate KITE-585 upon accidental injection. Simple contact exposure to blood from treated patients will not result in transmission of KITE-585, as KITE-585 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

NA

(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:

NA

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

The presence, expansion, persistence, and immunophenotype of KITE-585 cells will be monitored in the blood of treated patients primarily by PCR analysis, complemented by flow cytometry. Expansion and persistence in peripheral blood will also be monitored by quantitative polymerase chain reaction assay (qPCR). Blood will be collected according to Investigational product manual (IMP handling manual) and risk management plan.

Since KITE-585 comprises lentiviral vector transduced T cells, the presence of replication-competent lentivirus (RCL) in the blood of treated subjects will be monitored for up to 15 years. The risk of RCL is very low.

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 (m^2)
… m^2

NA

5. Duration of the monitoring

Monitoring will occur regularly for 5 years, and additional testing for RCL will be performed on samples obtained from patients treated with KITE-585 for 15 years.

6. Frequency of the monitoring

Blood samples will be taken at several time points after infusion: Week 2, Week 4, Month 2, Month 3, Month 4, Month 5, Month 6, and then every third month for the first two year, and every sixth month until year 5.

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 using a 70% ethanol solution. The patient's room after use will be cleaned using standard hospital cleaning and disinfection procedures with for instance a hydrogen peroxide solution (2% Aseptix) or per institutional guidelines.

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 GMO waste. All the surgical materials (surgery tools, linens) will be collected and autoclaved before washing or will be treated as and disposed of as GMO 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

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. KITE-585 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).

2. Methods for removal of the GMO(s) 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

NA.

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 KITE-585.

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