Application form

Assessment of clinical research involving gene therapeutics in the Netherlands

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Viral vectors

November 2017

Application form
Assessment of clinical study involving genetically modified viruses

Part A: Bio-safety aspects

A1. General information (Public section)
A2. Construction and composition (Public section)
A3. Production (Public section)
A4. Research description (Public section)
A5. Environmental risk assessment (Public section)
A6. Conclusions about possible environmental effects (Public section)
A7. General (personal) information (Confidential section)

Part B: Patient-related aspects (*not included in this form*)

If you have any questions, please get in touch with the Gene Therapy Office (E-mail: rik.bleijs@rivm.nl, phone: +31-30-2747569).

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Part A. Bio-safety aspects

This part of the application form provides the information needed for the Ministry of Infrastructure and Water Management (IenW) to grant the necessary licenses.

All information provided in this form and the accompanying documentation constitutes part of the decision to be made and for this reason is in principle open to inspection by the public; the information will also be available for such public inspection during the procedure.

The applicant may ask for parts of the information provided to be kept confidential. In that case, the applicant must give reasons why the information is of a confidential nature as well as a convincing explanation that the lifting of confidentiality will adversely affect the applicant's competitive position. A publicly available summary of confidential information must be given, containing enough information for a clear general understanding of the application and in order to assess the risk analysis as described in the application and the decision. Confidential information must be included in a separate attachment marked 'confidential'.

An application does not need to be limited to the specific clinical protocol that the applicant wishes to perform. If there are no consequences for the risk analysis, the application can be drawn up with a wider scope, such as for a larger number of patients.

The aim is to draw up the final decision in such a way that several clinical protocols can be performed under it, using the information described in this application. Naturally these activities must be covered by the description of the experiment and the risk analysis provided. Before submitting such a broader application, you are advised to contact the GMO office for an informal discussion of the options.

The term 'test subjects' as used in this form means patients or volunteers taking part in the study.

Specific personal details of the contact person and the environmental safety officer are to be submitted by entering the required information under Section A7, General (personal) information. The submitted data in this appendix will be kept confidential and will thus not be made publicly available in accordance with the Personal Data Protection Act.

This Notification Form may contain some questions that are not relevant to your case. We would ask you NOT to answer in your notification any questions that are irrelevant to the activities for which you are applying.

Specific issues:
- Literature that is referred to has to be sent in together with the application form.
- Confidential information has to be marked as such and has to be sent in separately.
- A SNIF B (other GMO) form has to be completed and to be sent in as an electronic file in Word format.

List of Abbreviations

Abbreviation	Definition
AIDS	Autoimmune deficiency syndrome
BCMA	B-cell maturation antigen
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CMV	Cytomegalovirus
COGEM	Commission on Genetic Modification (The Netherlands)
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
DLBCL	Diffuse large B cell lymphoma
EMA	European Medicines Agency
EU	European Union
FDA	United States Food and Drug Administration
Gag	Retroviral group specific antigen protein
G-CSF	Granulocyte colony stimulating factor
GMO	Genetically modified organism
GMP	Good manufacturing practice
HERV	Human endogenous retrovirus
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HSA	Human serum albumin
IV	Intravenous
LTR	Long terminal repeat
LVV	Lentiviral vector
MCB	Master cell bank
MHC	Major histocompatibility complex
MM	Multiple myeloma
MSCV	Murine stem cell virus
PCR	Polymerase chain reaction
qPCR	Quantitative PCR
RCL	Replication-competent lentivirus
RNA	Ribonucleic acid
RRE	Rev response element

Abbreviation	Definition
RRMM	Relapsed/refractory multiple myeloma
scFv	Single chain variable fragment
SIN	Self-inactivating
SNIF	Summary notification information format
USA	United States of America
VCN	Vector copy number
VSV-G	Vesicular stomatitis virus glycoprotein
WCB	Working cell bank
WPRE	Woodchuck post-translational response element

A1. General application details

General information

A1.1. Application title:

Clinical testing of KITE-585, an autologous cellular immunotherapy composed of T cells genetically modified ex vivo to express a chimeric antigen receptor (CAR) that, upon reinfusion into the patient, recognize and kill B-cell maturation antigen (BCMA)-expressing tumor cells.

A1.2. The objective of the study for which the application is submitted:

The goal of the KITE-585 clinical trial program is to assess the safety and efficacy of KITE-585 for the treatment of hematologic malignancies that express BCMA.

A1.3. Describe briefly the contents of the application, the objective of the study being aimed for and the intended application of the results

GMO: KITE-585 is a novel cellular immunotherapy, composed of autologous T cells engineered ex-vivo to express a CAR that targets BCMA expressed on the surface of malignant B-cells. Engineered autologous cell therapy is a process by which a subject's own T cells are collected and subsequently genetically engineered to express a T-cell receptor or a CAR specific for a target antigen expressed by specific malignancies (Johnson et al, 2006; Kochenderfer and Rosenberg 2013; Robbins et al, 2015). These engineered T-cell products represent a promising approach for cancer therapy (Holzinger et al, 2016).

Patient-derived T cells are transduced with a lentiviral vector (LVV) encoding the anti-BCMA CAR. It should be noted that the lentiviral transduction of T cells is done outside the European Union (EU). The shipped product does not contain LVV. Release specifications are discussed in A3.3.

Expected action: BCMA is a broadly expressed tumor antigen in B-cell malignancies such as multiple myeloma (MM). CARs are fusion proteins with antigen binding, transmembrane, and T-cell activation domains that, when expressed in T cells, can target tumor antigens for T-cell mediated killing. CAR T cells have demonstrated promising antitumor activity across B-cell malignancies, as re, including non-Hodgkin lymphoma (NHL) (Kochenderfer et al, 2012; Kochenderfer et al, 2015; Turtle et al, 2016; Kochenderfer et al, 2017a), acute lymphoblastic leukemia (ALL) (Davila et al, 2014; Maude et al, 2014; Lee et al, 2015; Maude et al, 2015; Singh et al, 2016) and chronic lymphocytic leukemia (CLL) (Porter et al, 2011; Kochenderfer et al, 2015; Porter et al, 2015)

The human BCMA gene codes for a 20 kDa, 184 amino acid cell surface transmembrane glycoprotein expressed during the differentiation of activated B cells to fully mature plasma cells in the bone marrow. BCMA functions to promote cell survival (Coquery and Erickson 2012) and its expression is tightly regulated in human tissues; BCMA is expressed in normal human plasma cells, certain B-cell subsets and plasmacytoid dendritic cells. Gene and protein expression profiling has shown that BCMA is also broadly expressed in MM cell lines and in primary MM cells (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, 2007a; Schwaller et al, 2007b; Khattar et al, 2017). Its limited normal tissue distribution combined with its broad expression in most patients with MM and potentially other hematologic malignancies makes BCMA a target to selectively kill tumor cells with KITE-585.

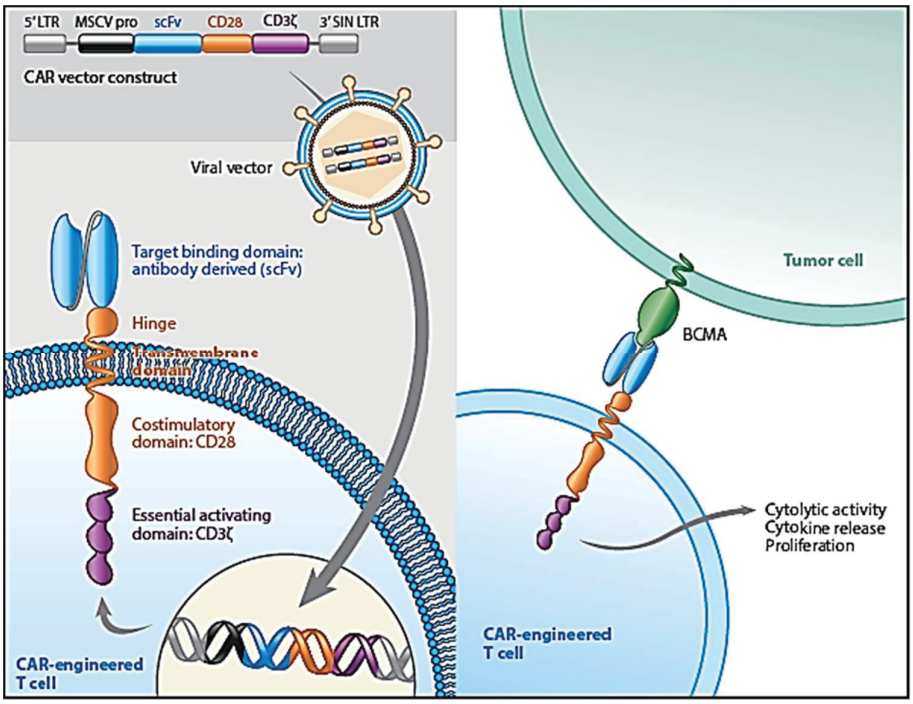
A review of the literature found that 100% of MM primary cells or cell lines expressed BCMA protein (70/70); using an alternate detection method by measurement of messenger RNA (mRNA), also found 100% of tested MM cells positive for BCMA mRNA (44/44) (Moreaux et al, 2004; Novak et al, 2004; Bellucci et al, 2005; Carpenter et al, 2013; Lee et al, 2016) and a Kite (Kite a Gilead Company, hereafter referred to as 'Kite') analysis of RNA samples in the Multiple Myeloma Genomics Portal found 91 of 92 samples expressed BCMA RNA (Zhan et al, 2006; Keats et al, 2007). In addition to its expression in MM, an analysis by Kite of DLBCL samples in the Cancer Genome Atlas also showed

clear positivity for BCMA RNA in the majority of DLBCL samples that would likely allow effective targeting of tumor cells with KITE-585.

Mechanism of action:

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 ζ; LTR, long terminal repeat; MSCV pro, murine stem cell virus promoter; scFv, single-chain variable fragment; SIN, self-inactivating.

Scientific and public importance of studies: Many hematologic malignancies have historically had relatively low survival rates, particularly in relapsed/refractory disease. Despite recent treatment advances, 10-year survival after a diagnosis of MM was 29% (Pulte et al, 2016). As reviewed by Kuruvilla and colleagues, approximately 20-30% of advanced HL patients relapse, and 10% of limited-stage HL patients are refractory to primary treatment; clinical trials demonstrate 17% to 45% CR rates in these patients, and median OS ranged from 40 to 90%, where reported (Kuruvilla et al, 2011). Approximately 30% to 40% of DLBCL patients have relapsed or refractory disease; median OS ranged from 4 to 13 months (Colosia et al, 2014). These malignancies all express BCMA on tumor cells, making them targets for anti-BCMA CAR T cells such as KITE-585.

Despite advances in the treatment of relapsed/refractory MM (RRMM), median progression-free survival and overall survival of patients treated with newer therapies remain unsatisfactorily short (6 to 12 months and 1 to 2 years, respectively), reflecting an unmet need for more effective therapies (Nooka et al, 2015).

A1.4. Describe briefly the intended work.

Production, transport, storage: The patients' T cells will be harvested by leukapheresis at the site and then will be transported for initial processing. Material will then be exported to Kite (California,

USA) for manufacturing of the final product. 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* and do not contain LVV) is manufactured it will be cryopreserved, and transported to the site of the European qualified person (EU QP) who will release the product. Transport will occur in a liquid nitrogen dry shipper, i.e., a shipper that is built with material that absorbs liquid nitrogen and leaves only the vapor phase. The product will then be transported to the clinical site according to good distribution practice (GDP). The Cell Therapy Facility, located in the Department of Pharmacy will take receipt of the GMO. The production of the GMO is not included in this license application. The license is being applied for the following procedures: receipt, thawing, and administration of the GMO, sample collection, handling of patient samples, and waste disposal.

Administration of the GMO, observation of patients and waste disposal: Receipt of the GMO will take place in the Cell Therapy Facility as mentioned above. After transporting the dry-shipper to the patient ward,Thawing in a water bath, and the administration of the GMO to the patient will take place in a patient room with restricted access in the hematology department at the UMC Utrecht. Medical personnel will wear gloves. GMO waste, including any waste that came in contact with the GMO, will be disposed of in the patient room in bins specified for hospital waste (UN 3291). Please refer to Section A4.9 for additional waste disposal information.

Sampling and sample analysis: Collection of patient blood, urine, bone marrow, cerebrospinal fluid (CSF), and other biopsy samples, where applicable, to be used for study purposes and/or routine patient care will take place at the department of Hematology, at the outpatient department or any other department, as necessary. These samples do not fall under the requirements for contained measures. The samples are not expected to contain viral particles and any genetically modified cells in the sample do not present a specific safety concern (see A2.17 and A5.2 to A5.5).

Waste treatment and disposal of unused material: Following handling and administration of KITE-585 to the patient, any unused residual compound remaining in the cryobag and all used materials that have been in contact with KITE-585 such as gloves and tubing will be disposed in an incinerator (A4.9).

A1.5. Intended start and end date:

KITE-585 will be studied in clinical trials for the treatment of BCMA-positive tumors between 01 January 2019 and 01 January 2049. These dates have been selected based on the initiation of clinical trials within the next 15 years and with follow up of patients, including sampling, throughout a maximum 15 year follow up period. During this time, 400 adult and pediatric patients with any BCMA-expressing cancer will be treated with KITE-585.

A.1.6. Do you want to keep other information confidential? If so, please specify in concrete terms how the release of the information would harm your competitive position.

No anti-BCMA CAR T-cell products are currently approved and therefore publishing the plasmid map, bioinformatics analysis, details of the manufacturing process, or the full release specifications would give a competitive advantage to other companies developing similar treatments.

A summary of the confidential information is included in the application to ensure a good general understanding of the information.

Details of applicant

A1.7. Name of legal entity:

Universitair Medisch Centrum Utrecht (UMCU)

A1.8. Chamber of Commerce (KvK) number:

30244197

A1.9. Visiting address of legal entity:

Heidelberglaan 100

A1.10. Postal code and town/city of location of legal entity:

3584 CX Utrecht

A1.11. At which locations will the intended work take place?

The intended work with the GMO will take place in the following UMCU locations:

Work with GMO	Location
Receipt of KITE-585	UMCU, The Cell Therapy Facility, located in the Department of Pharmacy
Treatment of patients with KITE-585 and collection of patient samples	UMCU Department of Haematology, outpatient department or other department at the UMC Utrecht
Analysis of patient samples	UMCU Cell Diagnostic Lab or external laboratory or external laboratory outside of The Netherlands

Abbreviations: GMO, genetically modified organism; UMCU, University Medical Center Utrecht.

Patient samples may be transported outside of The Netherlands to a Kite-authorized contract research organization for pre-specified analyses.

A2. Construction and composition of the GMO

Virus from which the genetically modified vector was derived

A2.1. Which virus was used as the original virus in the construction of the GMO?

Human immunodeficiency virus, type 1 (HIV-1) is the basis of the LVV delivery system of KITE-585 (the GMO).

Please note, the viral vector used in the manufacture of KITE-585 is a self-inactivating (SIN) replication-deficient LVV and is manufactured outside of the Netherlands. The autologous T cells are also engineered with the LVV outside of the Netherlands. Only the KITE-585 final product will enter the Netherlands. Free LVV is washed away from final product, with a reduction ratio well above that specified in COGEM guidance (A2.10). Because of the design of the lentiviral delivery system (A2.8), LVV particles can infect target cells once, but cannot infect additional cells after that. Even if an infectious particle survived long enough to infect an unintended cell in a patient, the self-inactivation would allow only a single unintended infection of a cell without further spreading.

A2.2. Describe how the identity of the original virus was determined.

Origin of the virus: The LVV used in the manufacture of the GMO is derived from HIV-1, strain HXB2.

Characteristics that determine the identity of the virus: The genome of wild-type infectious HIV-1 encodes the following 9 genes: *gag* (encodes a structural protein), *pol* (encodes a polyprotein that includes the protease, reverse transcriptase, RNase H and integrase), *env* (encodes an envelope glycoprotein that facilitates cellular entry of viral particles), *tat* (encodes a transcriptional activator), *rev* (encodes a protein that exports viral RNA to the cytoplasm), *vif* (encodes a protein that disables a cellular antiviral factor), *vpr* (encodes a protein that upregulates viral production), *vpu* (encodes a protein that enhances viral particle release), and *nef* (encodes a protein that induces down-regulation of host cluster of differentiation 4 (CD4) and major histocompatibility complex [MHC]). Six of these 9 native HIV-1 genes (vif, vpr, vpu, nef, env, and tat) are dispensable for lentiviral function, and have been removed from the LVV system (A2.8). The genes *gag/pol* and *rev* are encoded on separate helper plasmids to produce a replication-deficient LVV delivery system (A2.8). Additional regulatory sequences in wild-type, infectious HIV-1 include the long terminal repeats (LTRs) which are required for viral gene transcription. Rev protein binds the rev response element (RRE), facilitating the export of viral RNA to the cytoplasm. A psi packaging signal interacts with Gag to facilitate viral RNA genome incorporation into viral particles in the cell cytoplasm.

The vector backbone was fully sequenced by double stranded DNA primer walking. The vector insert containing the promoter and transgene was synthesized and cloned into the sequenced backbone. The sequencing results confirm that the original virus is HIV-1.

A2.3. What is the host range of the original virus?

Humans and possibly, chimpanzees, are the only natural hosts for wild-type, infectious HIV-1. HIV-1 mainly targets $CD4^+$ T cells, as well as dendritic cells, macrophages, microglia and other neurologic cells (Kallings 2008; King et al, 2013).

A2.4. Provide relevant data on pathogenicity and possible attenuation and biological restrictions of the original virus.

HIV-1 is classified as hazard group 3 (Commission on Genetic Modification [COGEM]). As with any virus, wild-type infectious HIV-1 is an intracellular pathogen and therefore its ability to replicate is completely dependent on the internal machinery of the host cell. HIV-1 has selective tropism against

certain human cell types. More specifically, its envelope restricts the virus infectivity primarily to $CD4^+$ T cells and macrophages. HIV-1 is typically present in certain bodily fluids of infected individuals, as free viral particles or in infected cells. This restricts HIV-1 transmission across individuals to the transfer of such fluids.

However, it should be noted that the viral vector used in the manufacture of KITE-585 is a SIN, replication-deficient LVV. Due to the multiple safety features of the LVV delivery system used, evidence of replication-competent lentiviruses (RCL) has not been observed in clinical trials of such vectors (Holzinger et al, 2016; Naldini et al, 2016; Cornetta et al, 2018). Additional discussion of the clean clinical record of LVVs in clinical use is provided in A5.1. Details are provided in A2.8 and A2.9.

A2.5. What are the pathogenic properties of the original virus and what are the available treatment methods?

Several weeks following initial exposure and infection by HIV-1, a patient may experience a brief episode of flu-like symptoms known as the acute retroviral syndrome. The infection then becomes a chronic and largely asymptomatic disease in which $CD4^+$ T cell numbers and function gradually decline. If left untreated, HIV infection leads to a near complete loss of CD4+ T cells, resulting in severe immunodeficiency and the onset of recurrent opportunistic infections, a condition known as acquired immune deficiency syndrome (AIDS) (Workowski et al, 2015). Progression to AIDS can be slowed or reversed with modern antiviral therapy, and many HIV-infected patients who are compliant with such therapy are able to live for decades without symptoms of the disease (Workowski et al, 2015).

A2.6. What are the transmission routes of the original virus?

Transmission routes for wild-type infectious HIV-1 are via sexual contact, maternal-infant exposure, and percutaneous inoculation with infected fluid, i.e., by needle stick or cutting of the skin or by contact with exposed skin that is chapped, abraded or afflicted with dermatitis (Shaw and Hunter 2012; Kuhar et al, 2013). Blood, tissue, or other body fluids such as semen and vaginal secretions are considered potentially infectious (Kuhar et al, 2013).

In contrast, the viral vector used in the manufacture of KITE-585 is a SIN replication-deficient LVV. Due to the multiple safety features of the LVV delivery system used, person-to-person transmission has not been observed in clinical use of these viral vectors (Holzinger et al, 2016; Naldini et al, 2016; Cornetta et al, 2018). Details are provided in A2.8 and A2.9.

A2.7. How could the original virus survive outside the host?

Although the risk of transmission by fluids is small (estimated at 0.3% by percutaneous exposure among health care personnel), wild-type HIV dried onto a surface can remain infectious for several days. The time required to reduce 90% of the virus on a dry surface is >70h (van Bueren et al, 1994; Kuhar et al, 2013).

The genetically modified viral vector

A2.8. Describe the 'original vector or vectors'.

The GMO comprises genetically modified T cells. Replication-deficient, SIN LVV is a starting material.

Overview of differences from wild-type HIV-1: To create a safe vector delivery system, 6 of 9 native HIV-1 genes (vif, vpr, vpu, nef, env, and tat) that are dispensable for lentiviral function, but that are required for wild-type HIV function, have been removed from the LVV system. The genes *gag-pol* and *rev* are encoded on separate helper plasmids to produce a replication-deficient LVV delivery system.

The vector is SIN because of deletions in the U3 region of both the 5' and 3' long terminal repeats

(LTRs), such that the ability to produce viral RNA from the viral LTR promoter is removed; thus, elements necessary for generating RCL are eliminated. Together, the absence of the HIV-1 accessory genes, coupled with removal of transcriptional elements in the 5' and 3' LTRs render the vector system replication incompetent.

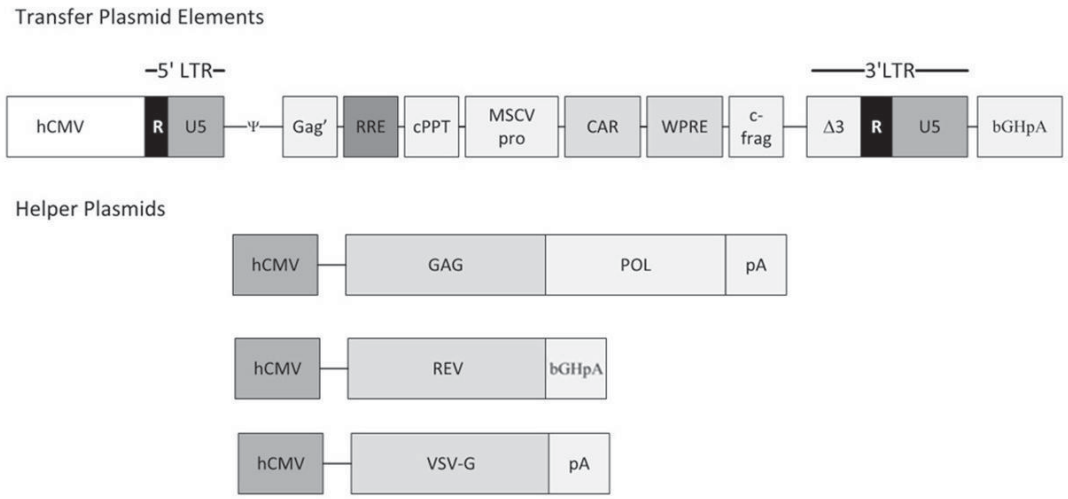
Similarly, the packaging and structural genes are not encoded by the LVV and are therefore not transferred to the target cells. Consequently, no viral proteins will be made by the transduced cells and therefore new vector particles cannot be formed. In contrast to wild-type HIV-1, the viral genome packaged in the KITE-585 vector has none of the viral machinery required to infect once the provirus has integrated into the final host cell.

Lentiviral delivery system: To increase the safety of the LVV system, essential components are split among four plasmids (the pLV-K585 transfer plasmid and three helper plasmids). A schematic diagram of the four-plasmid system illustrating the genetic structure of the LVV is shown in Figure 2. The transfer plasmid contains the transgene and essential cis-acting elements for reverse transcription, vector packaging, and integration of viral RNA into the target cell genome. The three helper plasmids consist of a plasmid containing the structural and enzymatic *gag*|*pol* genes, another plasmid expressing the Rev protein to facilitate export of the genomic RNA from the nucleus to the cytoplasm, and a third plasmid expressing the vesicular stomatitis virus envelope G protein (VSV-G). The VSV-G envelope allows for the efficient transduction of human cells (Sharma et al, 2000).

pLV-K585 Vector: To further ensure the safety of the vector delivery system, the *gag/pol*, and *rev* genes are not encoded by the LVV transfer plasmid (pLV-K585) but are contained on separate packaging plasmids (Figure 2). Essential features of the lentiviral transfer plasmid include the following elements:

1. A modified 5' LTR that exchanges the U3 region for the cytomegalovirus (CMV) promoter to drive the expression of the RNA viral genome in the packaging cell line
2. A packaging sequence (psi) contained within a truncated gag sequence (gag')
3. The HIV-1 RRE
4. A central polypurine tract
5. A murine stem cell virus (MSCV) promoter to drive the expression of the transgene within the target T cell. The MSCV promoter derived from the Moloney murine leukemia virus (MoMLV) LTR U3 region provides stable, high transgene expression levels in lentivirally transduced hematopoietic cells and T cells (Ramezani et al, 2000; Jones et al, 2009)
6. A woodchuck post-transcriptional regulatory element (WPRE)
7. C-frag, a synthetic DNA element that is not naturally occurring in humans that functions as a "DNA barcode" to identify the presence of the construct
8. A truncated 3' LTR (3'-SIN LTR) containing a deletion of the U3 region to prevent mobilization of the vector.
9. Bovine growth hormone polyadenylation signal terminates expression of the viral genome in the packaging cell line.

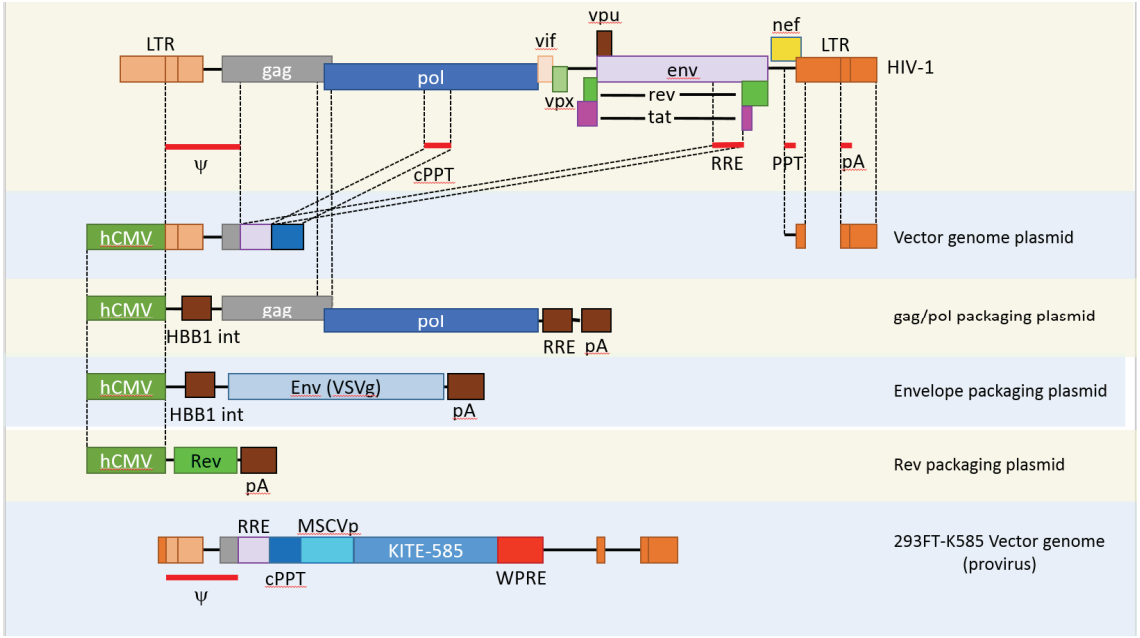
Figure 2. Schematic Diagram of the HIV-1 Based Vector System



Abbreviations: 3′ LTR (Δ3 R U5), a truncated 3′-SIN long terminal repeat containing a deletion of the U3 region to prevent mobilization of the vector; 5′ LTR (R U5), a 5′ SIN long terminal repeat that exchanges the U3 region for the CMV promoter to drive expression of the RNA viral genome in the packaging cell line; bGHpA, bovine growth hormone polyadenylation; CAR, chimeric antigen receptor; c-frag, unique non-coding marker sequence for identification of vector-transduced cells; cPPT, central polypurine tract; GAG, group-specific antigen; Gag′, truncated *gag* sequence; hCMV, human cytomegalovirus promoter; LTR, long terminal repeat; MSCV pro, murine stem cell virus promoter that drives the expression of the transgene within the target T cell; pA, human β globin polyadenylation sequence; POL, polymerase; Ψ, PSI packaging sequence; REV, Rev protein; RRE, HIV-1 rev response element; VSV-G, vesicular stomatitis virus envelope G protein; WPRE, woodchuck post-transcriptional regulatory element.

Shown in Figure 3 is a comparison of wild-type virus, the LVV, referred to as 293FT-K585 Vector, that is used to transduce T cells, and the provirus that is ultimately incorporated into T cells.

Figure 3. Comparison of the Genetic Structures of Wild-type HIV-1, the HIV-1 Based Lentiviral Vector, and the Proviral Elements Incorporated in KITE-585



Abbreviations: CAR, chimeric antigen receptor transgene; cPPT, central polyuridine tract; hCMV, human cytomegalovirus promoter; Env (VSVg), vesicular stomatitis virus envelope G protein; gag, group-specific antigen; HBB1 int, human beta-globin-Intron; LTR, long terminal repeat; MSCVp, murine stem cell virus promoter; pA, polyadenylation signal; pol, polymerase; Ψ, Psi packaging sequence; Rev, Rev protein; RRE, Rev response element; WPRE, woodchuck hepatitis virus post-transcriptional regulatory element.

Finally, in the generation of the LVV particles, the bacterial transfer plasmid contains a kanamycin resistance gene and a bacterial origin of replication; however, these are not a part of the LVV genome and are not incorporated into the GMO.

Please see Table 1 to 4, which describe the features and their origins for all 4 plasmids.

Table 1. **pLV-K585 Transfer Plasmid Features**

Element Identity	Description and functional Impact of intentional Changes	GenBank Accession/reference sequence, if any
CMV	Human cytomegalovirus (CMV) promoter is a constitutive mammalian promoter that drives high level expression of genomic RNA in packaging cells.	K03104.1 Human cytomegalovirus major immediate-early gene, enhancer
5'LTR*	Truncated 5' LTR that exchanges the U3 region for the cytomegalovirus (CMV) promoter.	K03455.1 HIVHXB2CG
NCR	Non-coding region (NCR) of HIV-1 origin.	K03455.1 HIVHXB2CG
PSI	Packaging signal sequence that is recognized by the nucleocapsid (NC) domain of the Gag polyprotein during virus assembly.	K03455.1 HIVHXB2CG
HIV-gag'	Truncated gag sequence which also contains GC insertion that leads to HIV-gag' frameshift and Stop codon for increased safety of the transfer vector. The environmental impact is increased safety of the construct in case of an unforeseen recombination event.	K03455.1 HIVHXB2CG
HIV-1 (HXB2) env sequences RRE	HIV-1 Rev response element (RRE) is a cis-acting RNA element essential for viral replication. RRE was identified in the envelope gene (env) of the HIV-1 viral genome. The env fragment within the transfer vector represents a fragment of the env gene and does not encode an open reading frame starting with a start codon.	K03455.1 HIVHXB2CG
cPPT/CTS	Central polypurine tract (cPPT) and termination sequence (CTS) provide increased transduction efficiency and transgene expression.	K03455.1 HIVHXB2CG
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic
MSCV	Murine stem cell virus (MSCV) promoter drives the expression of the transgene within the target T cell.	M17246.1 MSYPCMV
MCS	Multiple cloning site (MCS), non-coding region with no expected functional impact.	Synthetic
KITE-585 transgene	KITE-585 transgene open reading frame.	Synthetic
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic
WPRE	Woodchuck hepatitis post-transcriptional regulatory element (WPRE) contributes to higher transgene expression.	J04514.1 Woodchuck hepatitis B virus (WHV8)
MCS	Multiple cloning site (MCS), synthetic linker with no expected functional impact.	Synthetic

Element Identity	Description and functional Impact of intentional Changes	GenBank Accession/reference sequence, if any
cFrag	cFrag is a 100-base pair qPCR Id tag. This sequence element is not naturally occurring in humans and therefore can be used to detect integrated vector sequence in human cells.	Synthetic
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic
SV40 poly A enhancer I and II	SV40 derived poly A signal enhancer for improved termination of transgene transcription to prevent read through into the flanking genomic sequences	Synthetic
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic
HIV-nef'	HIV-nef' partial sequence which is a c-terminal nef segment extending into the 3'-SIN LTR and does not contain a start codon. Therefore, no functional nef protein can be generated.	K03455.1 HIVHXB2CG
3'-SIN LTR	Self-inactivating 3' LTR (3'-SIN LTR) is a truncated 3' LTR containing an extensive deletion of the U3 region which significantly improves the biosafety of HIV-derived vector, as it reduces the likelihood that replication competent retroviruses will originate in the vector producer and target cells.	K03455.1 HIVHXB2CG
MCS	Multiple cloning site (MCS), non-coding region with no expected functional impact.	Synthetic
bGHpA	Bovine growth hormone polyadenylation (bGHpA) signal is a specialized termination sequence for protein expression in eukaryotic cells.	NM_180996 Bos taurus growth hormone 1 (GH1)
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic
Kan/neoR	Kanamycin resistance gene allows for selection of plasmid-containing bacteria.	NC_022333.1
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic
ColE1 ori	Origin of replication allows initiation of plasmid replication in bacteria derived from E. coli plasmid pBR322.	pBR322 origin
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic

Table 2. pCMV-gag/pol Helper Plasmid Features

Element Identity	Description and functional Impact of intentional Changes	GenBank Accession/reference sequence, if any	Element position relative to plasmid origin
CMV	Human cytomegalovirus (CMV) promoter is a constitutive strong mammalian promoter that drives high level gene expression.	K03104.1 Human cytomegalovirus major immediate-early gene, enhancer	36..636
MCS	Multiple cloning site (MCS), non-coding region with no expected functional impact.	Synthetic	637..775
Beta-globin intron	Beta-globin intron derived from the human beta globin gene is used as an enhancer of transgene expression.	AH001475.2 Homo sapiens beta-globin gene	776..1279
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic	1280..1314
gag	Gag codes for the precursor gag polyprotein which is processed by viral protease during maturation to MA (matrix protein, p17); CA (capsid protein, p24); SP1 (spacer peptide 1, p2); NC (nucleocapsid protein, p7); SP2 (spacer peptide 2, p1) and P6 protein.	K03455.1 HIVHXB2CG	1315.. 2816
pol	Pol gene encoding viral enzymes reverse transcriptase (RT) and RNase H, integrase (IN), and HIV protease (PR).	K03455.1 HIVHXB2CG	2610..5618
MCS	Multiple cloning site (MCS), non-coding region with no expected functional impact.	Synthetic	5619..5646
RRE	HIV-1 Rev response element (RRE) is a cis-acting RNA element essential for viral replication.	K03455.1 HIVHXB2CG	5647..5878
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic	5879..6108
HBGpA	Human beta-globin polyadenylation (HBGpA) signal is a specialized termination sequence for protein expression in eukaryotic cells.	U01317.1 Human beta globin region on chromosome 11	6109..6797
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic	6798..7044
Kan/neoR	Kanamycin resistance gene allows for selection of plasmid-containing bacteria.	NC_022333.1	7045..7839
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic	7840..8087

Element Identity	Description and functional Impact of intentional Changes	GenBank Accession/reference sequence, if any	Element position relative to plasmid origin
ColE1 ori	Origin of replication allows initiation of plasmid replication in bacteria. The pUC ori is a mutated form of origin derived from E. coli plasmid pBR322 which allows production of greater than 500 copies of plasmid per cell.	pBR322 origin	8088..8770
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic	8771..35

Table 3. pCMV-rev Helper Plasmid Features

Element Identity	Description and functional Impact of intentional Changes	GenBank Accession/reference sequence, if any	Element position relative to plasmid origin
CMV	Human cytomegalovirus (CMV) promoter is a constitutive strong mammalian promoter that drives high level gene expression.	K03104.1 Human cytomegalovirus major immediate-early gene, enhancer	36..623
MCS	Multiple cloning site (MCS), non-coding region with no expected functional impact.	Synthetic	624..776
rev	Rev is a transactivating protein that is essential to the regulation of HIV-1 protein expression. A nuclear localization signal is encoded in the rev gene, which allows the Rev protein to be localized to the nucleus, where it is involved in the export of unspliced and incompletely spliced mRNAs.	K03455.1 HIVHXB2CG	777.. 1127
MCS	Multiple cloning site (MCS), non-coding region with no expected functional impact.	Synthetic	1128..1348
bGHpA	Bovine growth hormone polyadenylation (bGHpA) signal is a specialized termination sequence for protein expression in eukaryotic cells.	NM_180996 Bos taurus growth hormone 1 (GH1)	1349..1573
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic	1574..1745
Kan/neoR	Kanamycin resistance gene allows for selection of plasmid-containing bacteria.	NC_022333.1	1746..2540
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic	2541..2788
ColE1 ori	Origin of replication allows initiation of plasmid replication in bacteria. The pUC ori is a mutated form of origin derived from E. coli plasmid pBR322 which allows production of greater than 500 copies of plasmid per cell.	pBR322 origin	2789..3471

Element Identity	Description and functional Impact of intentional Changes	GenBank Accession/reference sequence, if any	Element position relative to plasmid origin
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic	3472..35

Table 4: pCMV-VSVg helper plasmid features

Element Identity	Description and functional Impact of intentional Changes	GenBank Accession/reference sequence, if any	Element position relative to plasmid origin
CMV	Human cytomegalovirus (CMV) promoter is a constitutive strong mammalian promoter that drives high level gene expression.	K03104.1 Human cytomegalovirus major immediate-early gene, enhancer	36..636
MCS	Multiple cloning site (MCS), non-coding region with no expected functional impact.	Synthetic	637..775
Beta-globin intron	Beta-globin intron derived from the human beta globin gene is used as an enhancer of transgene expression.	AH001475.2 Homo sapiens beta-globin gene	776..1279
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic	1280..1305
VSVg	Vesicular stomatitis virus glycoprotein (VSV-G) pseudotype provides for very broad vector tropism.	FJ478454 Recombinant vesicular stomatitis Indiana virus rVSV-G/GFP	1306.. 2841
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic	2842..3040
HBGpA	Human beta-globin polyadenylation (HBGpA) signal is a specialized termination sequence for protein expression in eukaryotic cells.	U01317.1 Human beta globin region on chromosome 11	3041..3729
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic	3730..3976
Kan/neoR	Kanamycin resistance gene allows for selection of plasmid-containing bacteria.	NC_022333.1	3977..4771
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic	4772..5019
ColE1 ori	Origin of replication allows initiation of plasmid replication in bacteria. The pUC ori is a mutated form of origin derived from E. coli plasmid pBR322 which allows production of greater than 500 copies of plasmid per cell.	pBR322 origin	5020..5702
NCR	Non- coding region (NCR), synthetic linker with no expected functional impact.	Synthetic	5703..35

A2.9. Regarding the pathogenicity of the original virus, have certain properties of the 'original vector' been altered that would determine the pathogenicity of the original vector?

Yes. The pathogenicity of HIV-1 and its ability to replicate have been ablated through the use of multiple safety features that have been incorporated into the LVV. First, the splitting of the viral genes into 4 separate plasmids reduces the likelihood of recombination resulting in RCL being generated.

Additionally, the 6 HIV-1 accessory genes (*vif*, *vpr*, *vpu*, *nef*, *env* and *tat*) that are essential for HIV-1 pathogenesis and replication have been deleted in the lentiviral system used in the manufacture of KITE-585. Although *env* is deleted, an envelope gene is needed for transfer into T cells, so the VSV-G *env* gene is used.

Finally, the ability of the virus to mobilize is removed by deletion of sequences from the long terminal repeat, i.e., the virus is SIN. These safety features are listed in Table 5.

Table 5. LVV Delivery System Safety Features

Safety Feature	Benefit
Deletion of HIV-1 genes *vif*, *vpr*, *vpu*, *nef*, *env* and *tat*	• *nef* appears to be a major pathogenic factor of primate lentiviruses. Expression of the nef protein in $CD4^+$ T lymphocytes, out of the context of viral infection, induces an AIDS-like disease in transgenic mice. During HIV infection, nef is likely to contribute to the immune escape of the virus by down regulating $CD4^+$ and MHC I molecules from the cell surface. • vif is responsible for the efficient *in vivo* infectivity of HIV-1 • vpu cooperates with nef in the downregulation of $CD4^+$ expression • vpr is important for macrophage infection as shown by the 50% decreased infectivity in the absence of vpr • tat is a crucial regulatory mediator required for the efficient transcription of HIV-1 genes
Distribution of essential HIV-1 genes onto four separate plasmids	The chance of RCL is very substantially reduced as multiple and sequential recombination events would be required for all 3 remaining viral genes to be integrated: 1. The transfer vector must recombine with the gag/pol plasmid RRE sequence restoring a LTR gag/pol ΔU3LTR. 2. The transfer vector must then recombine with the rev plasmid, restoring a continuous LTR-rev-ΔU3LTR. 3. The transfer vector must then recombine with the envelope plasmid, creating a continuous LTR-VSVg-ΔU3LTR. 4. The transfer vector must then re-acquire the promoter activity in the 3' ΔLTR which was deleted during generation of the vector plasmid DNA. The LTR promoter is not present in any of the plasmid DNAs, making it essentially impossible to recreate a functional virus. Most importantly all four recombination/repair events must involve the same molecule in order to generate a continuous LTR-gag/pol-rev-env-LTR.
SIN LTR	The ability to produce viral RNA from the viral LTR promoter is removed. • RCL cannot be generated unless the promoter activity of the LTR is restored • The possibility of mobilization of the transgene cassette by wild-type HIV infection is significantly reduced due to the

	lack of a functional LTR generated during reverse transcription through copying of the 3′-LTR to the 5′-terminus of the vector RNA that would transcribe the p17/Matrix portion at the 5′ end of the Gag gene, and upstream from the functional MSCV promoter that drives expression of the transgene The frequency of insertional gene activation is significantly decreased due to the lack of an active enhancer element in the LTR, ie, transcription of sequences downstream of the 3′-LTR is eliminated.
Minimal homology	Minimal sequence homology between the plasmids of the 4-plasmid system decreases the probability of a recombination event. Since overlapping sequences between plasmids or between the RNA molecules derived from the plasmids may increase the recombination frequency, plasmids were designed to minimize overlapping regions. Only a small number of overlapping sequence elements exist between the transfer plasmid and the helper constructs, as described: The CMV promoter is used in the transfer plasmid and in all 3 helper plasmids. However, recombination among CMV promoters could not render an RCL event. Such an event would generate constructs with the helper genes (*gag-pol* or *rev*) replacing the 5′ LTR. The 5′ LTR is required for RCL, so even if recombination were to occur, RCL could not result. A 389-bp region of identity exists between *gag′* (truncated *gag*) on the transfer plasmid and the *gag* gene on a helper plasmid. Also, a 230-bp region is identical between the RRE in the transfer plasmid and the RRE moiety in the gag-pol helper plasmid. The extent of these regions of identity is too small for efficient homologous recombination to occur. Additionally, subsequent recombination events for a total of 3 events involving the other helper plasmids would need to occur for the generation of RCL. It should be noted that in HIV-derived LVVs with identical design elements, no evidence of RCL has been observed in the clinic; see A5.1 (Holzinger et al, 2016; Naldini et al, 2016; Cornetta et al, 2018).

Abbreviations: CD4, cluster of differentiation 4; env, envelope glycoprotein; gag, group-specific antigen; HIV-1, Human immunodeficiency virus type 1 ; LTR, long terminal repeat; MHC, major histocompatibility complex; MSCV, murine stem cell virus; RCL, recombination competent lentivirus; RRE, Rev response element; SIN, self-inactivating; tat, transcriptional activator; VSVg, vesicular stomatitis virus G.

These alterations to the original vector make it highly improbable that RCL would be generated. In support of the safety of the LVV system used in KITE-585, no evidence of RCL in HIV-derived LVVs has been observed; see A5.1 (Holzinger et al, 2016; Naldini et al, 2016; Cornetta et al, 2018).

A2.10. Describe the method of production of the clinical viral vector from the 'original vector or vectors'.

The GMO comprises genetically modified T cells. Clinical viral vector, LVV, is the starting material. Manufacture of both the LVV and the GMO occurs outside the Netherlands.

Viral vector manufacture: 293FT-K585 Vector, a starting material that is absent in the KITE-585 final product, is produced transiently from the 293FT cell line. The cells are expanded in appropriate growth media. Once the desired cell count is reached, cells are transiently transfected with the transfer plasmid and three helper plasmids. Process-related impurities are removed with standard purification protocols. The 293FT-K585 Vector is sterile-filtered, and cryopreserved until ready to be used. Release of the vector requires passing predefined specifications (see A3.2).

KITE-585 manufacture: KITE-585 is generated from a patients' own T cells. T cells are enriched from the patient's blood, transduced with the 293FT-K585 Vector that contains the anti-BCMA CAR, and expanded through a series of carefully controlled steps. KITE-585 is not released unless it meets release specifications, including absence of RCL (A3.3).

The Kite manufacturing process ensures LVV is inactivated and removed during production of the GMO by two different means. First, LVVs with the VSV-G pseudotype are relatively unstable when cultured at 37°C, with a half-life of just over 10 hours. Thus, after 7 days at 37°C, approximately 99.99% of the LVV would be inactivated (Higashikawa and Chang 2001). Thus, the manufacturing process would be predicted to inactivate any residual LVV particles.

Second, during cell manufacturing, LVV is removed by a number of wash steps. COGEM recommends a calculation of the "reduction ratio" for determining the level of free viral particles remaining after purification of a cellular product (CGM/090331-03), since this cannot be directly assayed. The calculation uses the initial number of viral particles, the number of viral particles remaining after the purification protocol, the number of wash steps, the number of inactivation steps with either trypsin or human serum, and the number of days in culture to determine the reduction ratio.

The COGEM guidance-specified clearance of a lentiviral product using the reduction ratio formula is as follows:

Reduction ratio (Lentiviral vectors) = $(20^{W} \times 200^{I} \times 2^{2.4T})/Ci$

Where

W = number of wash steps

I = number of inactivating wash steps with trypsin or human serum

T = number of days in culture

2.4T = half-lives per day x number of days in culture

Ci = number of viral particles added

Reduction ratio for KITE-585 manufacturing process is calculated as follows:

W = number of wash steps = 5

I = number of inactivating wash steps with trypsin or human serum = 0

T = number of days in culture = 7

2.4T = half-lives per day x number of days in culture = 16.8

Ci = number of viral particles added = 2.5×10^{9}

Please note that the number of days the LVV spends in culture is from the time of the transduction of the T cells with LVV. This transduction step takes 1 day. Expansion then subsequently occurs for a minimum of 6 days after that, for a total of at least 7 days in culture and up to a total of 8 days in culture, depending on the time it takes to obtain the desired number of cells. The minimum number of days the LVV in culture is therefore the sum of the transduction (1 day) and expansion steps (6 days), ie, 7 days.

Using the above reduction ratio formula, the calculated viral reduction ratio for the KITE-585 manufacturing process of 146 is a theoretical estimate of viral clearance that exceeds the COGEM guidance for a viral reduction ratio of 100, indicating that there is less than a 1% chance that the product contains a viable vector particle. Kite estimates that this is a conservative number, as this calculation does not take into account the cell expansion phase with media perfusion that is part of the manufacturing process. Along with the removal of impurities by perfusion, additional inactivation and clearance of the 293FT-K585 Vector will occur when the LVV is exposed to contact surfaces for ≥ 6 days. Thus, residual infectious LVV is considered to be negligible in KITE-585.

A2.11. Describe the coding genes and the regulatory sequences present in the vector and in the DNA inserted into the vector.

The coding gene is the CAR transgene, which is transcriptionally regulated by an MSCV promoter and a WPRE. Other regulatory sequences consist of a CMV promoter and minimal lentiviral sequences.

Elements of the provirus, ie, genetic elements incorporated to the GMO: The transfer vector, referred to as pLV1-K585, contains the following elements that ultimately are incorporated to CAR T cells (Table 6; Figure 3): 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. The CAR transgene is composed of the elements in Table 7. There are no vector elements for which the origin or function is unknown. A comparison of the two sequences to the reference sequence demonstrates a 100% match.

Table 6. 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	Encodes the CAR transgene
WPRE	Sequence derived from woodchuck hepatitis virus improves stability and expression of the CAR transgene, while minimizing read-through of the promoter

Element	Description (and origin, where applicable)
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.

Table 7. 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 a short linker 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

A2.12. Provide a molecular characterization of the genetically modified viral vector.

Bioinformatics analysis of sequence: The lentiviral vector (LV) components in the transfer plasmid utilized to generate the lentiviral vector were derived from HIV-1 (HXB2, GenBank: K03455.1). In order to provide increased safety, the Lentigen transfer plasmid backbone is engineered with specific sequence alteration of a 2 base pair insertion leading to HIV-gag' frameshift and stop codon, and generation of the 3' SIN LTR (Schambach et al, 2013). Therefore, the resulting transfer plasmid sequence is not 100% match to the HIV-1 (HXB2, GenBank: K03455.1) reference, however the changes are expected.

The identity of the transfer and helper plasmids is verified by double-stranded primer-walking sequencing performed as a release assay for GMP plasmid DNA manufacturing and it is completed before the KITE-585 vector manufacturing process.

The expected integrated sequence of the LV is based on the nucleotide sequence of the KITE-585 transfer plasmid and after LV particle manufacture and subsequent transduction of cells, the vector genomic RNA undergoes reverse transcription (Hu and Hughes 2012) to form proviral DNA which then integrates into the chromosome of the targeted cell. DNA is isolated from the transduced cells and Sanger sequencing is used to confirm identity of the sequence of the integrated vector. Sequencing data of KITE-585 vector integrated into the genome of 293FT cells were compared with the expected integrated sequence. No mutations were discovered when obtained and a 100% match was reported. Therefore, there are no unexpected changes in relation to the associated expected integrated sequence and no impact on the environmental assessment. Details of the pLV-K585 transfer plasmid features, including the reference sequences utilized, description and functional impact of the intentional changes can be found in Table 1.

A2.13. Describe the origins of the cells/cell lines in which the original viral vector is cultivated. Also indicate which of the genetic components of the cell could possibly cause complementation or recombination.

The 293FT cell line used in the manufacturing of the LVV is a fast growing, highly transfectable subclone of the 293 cell line that contains the simian virus 40 (SV40) large T antigen. Studies have demonstrated maximal lentiviral production in 293 cells that express SV40 large T antigen (Naldini et al, 1996).

The parental 293 cell line is a permanent line established from primary embryonal human kidney transformed with sheared human adenovirus type 5 DNA. The E1A adenovirus gene is expressed in these cells and participates in transactivation of some viral promoters, allowing these cells to produce very high levels of protein.

The 293F cell line is a fast-growing variant of the 293 cell line, and was originally obtained by Invitrogen from Robert Horlick at Pharmacopeia. The 293FT cell line is derived from the 293F cell line and stably expresses the SV40 large T antigen from the pCMVSPORT6TAg.neo plasmid. This plasmid has been modified to include the following features:

- The neomycin resistance gene for selection of stable transfectants in mammalian cells. Expression of the neomycin resistance gene is controlled by the SV40 early enhancer/promoter from which the SV40 origin of replication has been removed.
- The gene encoding the SV40 large T antigen to facilitate optimal virus production and to permit episomal replication of plasmids containing the SV40 early promoter and origin. Expression of the SV40 large T antigen is controlled by the human CMV promoter.

Not all constituents of SV40 virus are present in the 293FT cell line during vector production and packaging. Thus, live SV40 virus cannot be reconstituted in the LVV final product or in KITE-585. Nevertheless, as a safety precaution, as a release assay for the lentiviral vector the SV40 large T antigen is measured in the final LVV product.

Lentigen's transfer plasmid backbone only contains a dimer of the SV40-derived poly A signal enhancer downstream of the transgenic cassette; this sequence element is included for improved termination of transgene transcription to prevent read-through into the flanking genomic sequences.

The KITE-585 transfer plasmid and helper plasmids do not contain SV40 origin of replication and there are no other sequence elements of the SV40 virus origin present in these plasmid backbones. The 293FT master cell bank (MCB) was developed at Omnia Biologics (Rockville, MD). A 293FT working cell bank (WCB) was used for good manufacturing practice (GMP) manufacturing of the 293FT-K585 Vector. The 293FT WCB was developed from the MCB at Lentigen Technology, Inc. (Gaithersburg, MD). One vial of the MCB (passage 5) was thawed, expanded for an additional 3 passages (passage 8) over 10 days, and then vialed and cryopreserved. Both the MCB and WCB are extensively tested to ensure sterility, and must show an absence of viral contaminants and adventitious viruses for release. The MCB is tested for a panel of viruses including HIV, human T-lymphotrophic virus (HTLV), and hepatitis C (HCV), and all tests must be negative for release. Thus, there is no virus with which the vector could recombine.

Human endogenous retroviral sequences (HERVs) are retrotransposons with retrovirus-like sequences present in the human genome. They account for about 8% of the human genome, have been present for up to millions of years, and are replication incompetent (Stoye 2012). HERVs identified to date are homologous to β retroviruses and γ retroviruses, but not lentiviruses (Dewannieux and Heidmann 2013). Given the low sequence homology and small percentage of lentiviral DNA in the 293FT-K585 Vector, recombination is considered extremely unlikely. No RCL has been reported in clinical experience with lentiviruses (Holzinger et al, 2016; Naldini et al, 2016; Cornetta et al, 2018). The WPRE, a ~600-nucleotide element derived from woodchuck hepatitis virus, is a hepadnavirus similar to hepatitis B. No endogenous retroviruses (ERVs) are derived from hepadnaviruses in the

human genome, although other mammals contain hepadnavirus-derived ERVs (Honda 2017). Given their genetic similarity, recombination of the WPRE with endogenous hepatitis B virus (HBV) might be possible. However, it should be noted that HBV post-transcriptional regulatory elements and the WPRE, with 200 interspersed mismatches and a gap of 16 contiguous bases out of 607 base pairs (Galibert et al, 1982) do not share extended domains of identity (58% homology) thus making recombination less likely in the context of HBV infection. Nevertheless, as a precaution, active or chronic hepatitis B infection is an exclusion criterion for clinical treatment in the KITE-585 program, as are infections with other viruses that have reverse transcriptase activity (HIV, hepatitis C virus [HCV], HTLV). There are no HTLV-derived elements used in the LVV used to generate anti-BCMA CAR T cells. Subjects are not screened for HTLV-1 because the seroprevalence of HTLV-1 in Europe is very low. European seroprevalence rates are < 0.4 per 10,000 among first time blood donors with the exception of Romania, which has a rate of 5.3 per 10,000 in first time blood donors (Gessain and Cassar 2012). For perspective, across Europe, HTLV prevalence, at 0.4 cases per 10,000, is more than 10-fold lower than the cutoff for rare diseases designation, which is 5 cases per 10,000 persons. Furthermore, since the year 2000, Romania has performed routine screening for HTLV of blood donors, leading to a continued decline in HTLV-1 prevalence. (https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/MER-Romania-2010-country-mission.pdf). Importantly, potential subjects in KITE-585 studies known to be HTLV-positive will be excluded from the studies, thus minimizing any theoretical risks of recombination between HIV-1 components of the lentiviral vector, and HTLV-infected persons.

The LVV used in the manufacture of KITE-585 is not anticipated to be a contaminant in final product, and the current manufacturing process conforms to and exceeds COGEM standards, with a reduction ratio well above the minimum of 100 ($RR_{KITE-585}$ = 146, see A2.10); thus it is deemed unlikely that LVV and HTLV would ever encounter each other in subjects treated with KITE-585.

The mechanism that would be relevant for theoretical recombination events between HIV elements present in the LVV used to manufacture KITE-585 and HTLV is homology-mediated RNA template switching. This is a well-characterized natural process in the context of two retroviral infections present in an individual at the same time (dual infections) (Goodrich and Duesberg 1990). In active dual retroviral infections, there are thousands of virions produced per cell; in contrast, in the context of KITE-585 treated subjects, the number of LVV particles present is expected to be negligible since they are not anticipated in the final product. Nevertheless, a sequence analysis performed between the LVV and HTLV-1 (accession NC_001436.1; 8507 bp) showed low sequence homology between the LVV used in the manufacture of KITE-585 and HTLV-1 (Kite Pharma, data on file). More specifically, the sequence similarity analysis found 6 regions of 49% to 54% identity, of 392 to 1007 bps in length (for perspective, 25% would be expected in two random, unrelated sequences). Within these regions, however, there are no stretches of continuous homology (identical bases with no skips) longer than 12 bps. There is a single 12-bp region of identity, and after that, the longest stretch of continuous identical bases is 7 bps long. This is important because recombination during template switching requires a minimal number of bases, around 14 bps of continuous complementary bases for efficient recombination (Pfeiffer and Telesnitsky 2001). Based on these considerations, Kite considers that this poor level of homology represents a very low likelihood of recombination even if LVV particles and HTLV-1 viral particles were to comingle. In addition, excluding individuals with known HTLV infection from the clinical studies, coupled with negligible levels of LVV present after manufacturing, make the likelihood of recombination even more remote.

Finally, it should be noted that recombination during vector production is very unlikely because of the 4 different plasmids used in the packaging system and lack of homology between the helper plasmids and transfer vector (Cesani et al, 2015).

Nevertheless, all clinical studies of KITE-585 will employ a robust monitoring plan to assess the presence of RCL in the product and in subjects' blood before and after infusion of KITE-585. Testing of LVVs for RCL will be performed according to the European Medicines Agency (EMA) Guideline on Development and Manufacture of Lentiviral Vectors (CHMP/BWP/2458/03; 2005), which provides general guidance on RCL testing assays. Testing will also be performed in accordance with FDA Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors (November 2006), which provides additional recommendations on stages of manufacture at which to

test, and recommendations on patient testing schedule and assays after administration of gene therapy. Given that there is no conflict between these recommendations, Kite will be following the EMA guideline. The presence of RCL in the blood of treated patients will be monitored for 15 years.

In conclusion, 293FT cells do not contain any component of the LVV in their genome or any other sequence closely homologous to it, minimizing any chance of complementation or recombination.

A2.14. Summarize the data in a diagram ('map') of the genetically modified organism. Also indicate any relevant helper sequences that may possibly be present.

Information on the inserted genetic elements in the GMO is provided in Figure 3 (A2.11). Only the sequence elements between the 5' and 3' LTRs is incorporated to T cells (Figure 2).

A2.15. Indicate the degree to which the host range of the genetically modified viral vector has been or may be altered, relative to the original virus.

The LVV delivery system has been altered to use a viral envelope protein 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, T cells, rat fibroblasts, and terminally differentiated neurons (Naldini et al, 1996). By contrast, wild-type, infectious HIV-1 is restricted to $CD4^+$ T cells, as well as dendritic cells, macrophages, microglia and other neurologic cells (Kallings 2008; King et al, 2013).

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). Additional information is provided in A4.8 and A5.3.

A2.16. What physiological (including pathogenic) effects may be caused by the genetically modified viral vector; and what are the available treatments?

Vector: Product release of KITE-585 requires the absence of RCL. If free lentiviral particles were somehow to be present as an impurity in a KITE-585 preparation, LVV particles could theoretically establish latency in individual host cells. Because the LVV is replication-defective, it could not shed or spread further. If the LVV were to establish latency in a small number of host cells, it would not confer selective advantage to the cells, or be predicted to cause deleterious effects.

The GMO: The following adverse events are considered important potential risks with KITE-585: cytokine release syndrome (CRS), neurologic events, cytopenias, infections, and tumor lysis syndrome (TLS). It should be noted that these potential risks are unrelated to the pathogenesis of wild-type HIV-1; rather, they are, effects that are known to be associated with the conditioning chemotherapy and/or the mechanism of action CART cells, as described below. Theoretical risks include secondary malignancy and generation of RCL, although neither of these potential risks has been attributed to LVVs in the clinic (Holzinger et al, 2016; Naldini et al, 2016; Cornetta et al, 2018).

Cytokine release syndrome: CRS is a symptom complex associated with the use of monoclonal antibodies and immune-activating therapies, such as CAR T cells used for treatment of patients with B-cell lymphomas and leukemias (Kochenderfer et al, 2017a; Kochenderfer et al, 2017b; Neelapu et al, 2017a; Neelapu et al, 2017b; Shank et al, 2017) and in patients treated with anti-BCMA CAR T cells (Ali et al, 2016; Berdeja et al, 2017; Cohen et al, 2017). CRS results from the widespread activation of both immune and non-immune cell types. During CRS, cytokines and other immune effector molecules are found in high concentrations in the serum and are believed to cause the characteristic constellation of signs and symptoms that define CRS, including fever, hypotension, tachycardia and hypoxia. More severe symptoms may include cardiotoxicity, vascular leak syndrome, acute renal failure, and other organ dysfunction (Lee et al, 2014). Administration of the IL-6 receptor antagonist tocilizumab has been shown to improve the signs and symptoms of CRS and is approved for the treatment of CRS by the USA FDA (Davila et al, 2014; Lee et al, 2014; Neelapu et al, 2017a).

Neurotoxicity: Neurologic events (eg, encephalopathy, cerebral edema, somnolence, aphasia) have been observed with the bispecific CD19-directed CD3 T-cell engager blinatumomab (Topp et al, 2015) and with anti-CD19 CAR T-cell therapies (Brudno and Kochenderfer 2016). Early reports of studies

using anti-BCMA CAR T cells have also detailed neurologic events (Ali et al, 2016; Cohen et al, 2016). The recommended management of neurologic events includes tocilizumab, when symptoms of CRS accompany neurologic events, and corticosteroids in the absence of CRS.

Cytopenias and Neutropenic Fever: Many patients are expected to experience decreased blood counts and neutropenic fever, primarily resulting from transient and reversible bone marrow suppression due to the conditioning chemotherapy regimen (fludarabine + cyclophosphamide). Additionally, many patients with RRMM have high marrow-burden disease and have received numerous prior myelosuppresive therapies, each of which may impact peripheral blood counts. Blood product and growth factor (granulocyte colony-stimulating factor [G-CSF]) are used to manage cytopenias per established clinical guidelines. Neutropenic fever should also be treated with empiric antibiotics and other supportive measures per established clinical guidelines (Klastersky et al, 2016).

Infections: Infections are expected due to the conditioning chemotherapy regimen. Prophylaxis is recommended. Evaluation for a source of infection should be performed.

TLS: TLS has the potential to develop in any subjects with significant malignancy burden, particularly when treated with efficacious anti-tumor therapies. Prophylactic treatment (e.g., allopurinol) is advised prior to initiation of conditioning chemotherapy.

Secondary malignancy: There exists a theoretical concern that transduction of autologous cells with LVVs may give rise to gene disruption caused by the integration of retroviral DNA into loci that could result in oncogenesis (Nienhuis et al, 2006). Malignancies caused by insertional mutagenesis were reported with early retroviral therapy that used retrovirally-transduced hematopoietic stem cells, which are a less differentiated cell type that is more prone to oncogenic transformation compared to mature T cells (Levine et al, 2006; Cartier et al, 2009; Cavazzana-Calvo et al, 2010; Aiuti et al, 2013). No case of malignancy has been reported to date for patients treated with LVVs. In accordance with current FDA thought and to minimize possible insertional mutagenesis, a vector copy number (VCN) limit of 5 or fewer per cell is implemented for final product release of KITE-585 (Zhao et al, 2017). Should insertional oncogenesis occur, standard-of-care treatments would be administered for the particular secondary malignancy observed.

A2.17. Indicate the possible transmission routes of the genetically modified viral vector.

The viral transduction is performed outside of the Netherlands. The final cell suspension product does not contain infectious viral particles anymore. Even if a very low number of infectious viral particles would be present in the KITE-585 cell product, the vector is replication-deficient and could only integrate once and no further spreading is possible. In addition, any remaining vector will be inactivated by the complement component of human serum after administration to the patient or accidentally to an unintended recipient. The predicted habitat of the genetically modified cells is only the patient which the cells were derived. Factors that may allow release of the KITE-585 cells outside the restricted host are blood tests and accidental injury. If these occur, there is no risk to the environment as KITE-585 does not survive in the environment and is rapidly inactivated by standard means of disinfection. Any released KITE-585 cells cannot be transmitted by air, but could be transferred through accidental injection or contact with broken skin. Medical personnel (or other individuals), if exposed to KITE-585 through accidental injection of minimal numbers of KITE-585 cells, would eliminate the cells via their immune system and not experience adverse effects beyond a normal immune reaction. Thus no negative consequences in this case.

A3. Production of the GMO

A3.1. State under whose responsibility the production of the GMO is carried out.

Answer:

O Production will be under the responsibility of the applicant and forms part of this license application.

O Production will be by and under the responsibility of the applicant but does not form part of this license application:

- O A separate application for production will be submitted for contained use
- O Reference is made for the production to an existing license for contained use: (State here the number of the relevant GMO license)

X Production will be under the responsibility of third parties. If production is in the Netherlands, please state the number of the relevant GMO license. Please state if production is outside the Netherlands.

Production of KITE-585 will take place outside of the EU and under the responsibility of Kite, located in the USA.

A3.2. During which steps of the production process does quality control take place, which test methods are used and how are the tests carried out?

Quality control tests are performed at all stages of the KITE-585 manufacturing process, from manufacture of 293FT-K585 LVV to KITE-585 final product release. All steps are carried out under GMP.

QC of the vector: The 293FT-K585 Vector is tested for identity and presence of transgene, and must be free of mycoplasma, viruses, and RCL and must meet acceptance criteria for sterility, and endotoxin.

QC of the GMO: KITE-585 is manufactured using each patients' individual T cells transduced with the 293T-K585 Vector, using an overall control strategy designed to ensure product quality and consistency. Release specifications require:

- Identity by specific amplification of the KITE-585 transgene by qPCR. The primers and probe of this assay are directed at the scFV ADI21530 heavy chain. Acceptance criteria is positive amplification, 100% sequence identity is not required
- Sterility by BacT/ALERT® 3D and absence of mycoplasma by qPCR
- Negative gram stain
- Endotoxin levels are below specification limits
- Absence of RCL by qPCR: RCL testing is performed at release of KITE-585 final product.

  RCL will be assessed with qPCR, the detection limit of the assay is 10 copies of the GMO per 200 ng of genomic DNA. Specific primers designed to amplify VSV-G, the viral envelope gene and the viral GAG-POL gene are used to detect the presence of RCL. The VSV-G and *gag-pol* genes are present only on the helper plasmids (Figure 2). Thus, the genes will only be detected if a recombination event has occurred.

A3.3. Which criteria are imposed on a batch of the GMO before it is released for the application in question?

KITE-585 final product undergoes rigorous testing to ensure it is free of RCL, bacteria that produce endotoxin, mycoplasma, and other microbes. A summary of the release testing for the GMO and in-process quality control testing is provided in A3.2.

A summary of the release testing is as follows:

- Identity by specific amplification of the KITE-585 transgene by qPCR. The primers and probe of this assay are directed at the scFV ADI21530 heavy chain. Acceptance criteria is positive amplification, 100% sequence identity is not required
- Potency is determined as the percentage of cells expressing the CAR transgene (by flow cytometry), and measurement of biological functionality in response to BCMA-expressing target cells (IFN gamma production)
- VCN by qPCR
- Sterility by BacT/ALERT® 3D and absence of mycoplasma by qPCR
- Negative gram stain
- Endotoxin levels are below specification limits
- Absence of RCL by qPCR: RCL testing is performed at release of KITE-585 final product.

  RCL will be assessed with qPCR. Specific primers designed to amplify VSV-G, the viral envelope gene and the viral GAG-POL gene are used to detect the presence of RCL. The VSV-G and *gag-pol* genes are present only on the helper plasmids (Figure 2). Thus, the genes will only be detected if a recombination event has occurred.

A4. Description of the research

Administration

A4.1. How many test subjects will take part in the study?

A maximum of 400 adult and pediatric patients with any BCMA-expressing cancer will be treated in clinical trials with KITE-585.

A4.2. Describe how the batch containing the GMO will be transported and prepared for administering to the test subjects.

As described in A1.4, the manufactured and purified autologous KITE-585 T-cell product is shipped from Kite (California, USA) to the site of the EU QP, who will release the product across the countries in Europe. In addition to the Netherlands, other countries to which KITE-585 may be shipped include Germany, France and the United Kingdom.

A general description of the storage and administration are provided below:

KITE-585 is supplied cryopreserved in cryostorage bags. The cryostorage bags containing KITE-585 arrive frozen in a liquid nitrogen dry shipper. The dry shipper is stored at the UMCU Cell Therapy Facility in a restricted area. The bags must remain frozen until the patient is ready for treatment to assure viable live autologous cells are administered to the patient. Several inactive ingredients are added to the product to assure viability and stability of the live cells through the freezing, thawing, and infusion process. The dry shipper is transported to the patient room at the hematology ward. The bag with the frozen cells will be taken out of the shipper and transferred to a second bag so in the case of a leakage of the cryostorage bag the cells will be contained. The cells are thawed in a water bath and the infusion bag is connected to the infusion line via a closed system.

KITE-585 is a patient-specific product and the intended patient will be identified by a unique patient ID number. Upon receipt, verification that the product and patient-specific labels match the patient's information (e.g., site number, patient ID number) is essential. The product must not be thawed until the patient is ready for the infusion. The thaw start/stop time will be noted in the patient medical record.

A4.3. How will the GMO preparation be administered to the test subject?

Patients will be administered KITE-585 by IV infusion using non-filtered tubing either by gravity or with an intravenous (IV) pump with a flow regulator. The cryobag is accessed by direct spiking with the non-filtered tubing. Central venous access such as a port or a peripherally inserted central catheter is required for the administration of KITE-585 and for the treatment period.

KITE-585 is patient-specific, that is, it is derived from the patient's own T cells.
Prior to administration of KITE-585, the product label will be checked by two personnel at the research site and asked to complete the Kite Countersignature Form.

Even though KITE-585 is not pathogenic and does not replicate, exposure to the product will be restricted to the patient. The personnel handling the product bags containing KITE-585 will follow universal precautions for body fluids (Siegel et al, 2007) and the following standard procedures for cell therapy. The number of other individuals present in the room at the time of administration is limited. Absorbent material covers the patient near the administration site in case of spills, and plastic slipcovers protect the bed to avoid contamination from a possible spill. Protective coat and gloves are to be worn by medical personnel during administration. No additional safety measures will be taken for KITE-585 handling and infusion.

A4.4. Which doses will be administered and at what time points during the study will they be administered?

For the first clinical use of KITE-585 in The Netherlands, KITE-585 will be administered as a single dose, with a maximum of 1 x 10^9 anti-BCMA CAR T cells. However, this dose may be increased and multiplied in future clinical trials or applications. The cumulative dose of KITE-585 per patient will not exceed 2 x 10^9 anti-BCMA CAR T cells.

A4.5. What other medication will be administered to the test subject that may possibly affect the GMO to be administered?

Subjects receive conditioning chemotherapy several days before the KITE-585 infusion, and necessary premedications immediately prior to the thawing and infusion of KITE-585. Following infusion, no additional medications that could affect the GMO are required per protocol. If a subject experiences toxicity such as symptoms of CRS, due to the activity of KITE-585, the subject may be treated with medications such as tocilizumab and/or corticosteroids that are intended to reduce the toxicity. In the case of corticosteroids, these drugs are known to be toxic to and may cause the death of lymphocytes, which is the primary cell type in KITE-585. However, administration of these concomitant medications will not increase the risk of the GMO to the subject or to the environment as RCL are not contained in the GMO and are not expected to be released at any point following KITE-585 infusion.

Sampling

A4.6. Describe which of the samples taken from the test subject may contain GMOs.

Blood, bone marrow, urine, tumor tissue, and CSF samples may be taken from patients during short- and long-term follow-up. Although these samples would not contain RCL (see safeguards discussed in A2.8 and A2.9) and are highly unlikely to contain LVV (A2.10), the samples may contain the GMO, i.e., engineered T cells. Patients' engineered T cells are not pathogenic, and do not replicate or survive outside the patient.

A4.7. Describe the method of sampling and how the samples will be subsequently processed.

Sampling of blood, bone marrow, urine, tumor tissue, and CSF, where applicable, will be performed by experienced hospital and laboratory personnel.

To avoid contamination of staff or the environment by these tissues and fluids, the sample collection will be performed with closed tube system and sterile/aseptic technique and used materials (ie, needles) will be disposed as specific hospital waste (UN3291; see A4.9). At each scheduled follow-up visit after KITE-585 final product infusion, approximately 50 mL of blood sample will be drawn from the patients to perform local and central laboratory assessments.

Patient samples will either be determined directly, or may be transported outside of The Netherlands to a Kite-authorized contract research organization for pre-specified analysis. Local analysis, processing, and storage will be done at a standard diagnostic laboratory of the center, as the samples do not contain viral particles (A4.6) and any GMO present in the samples do not represent a specific safety concern (A2.17 and A5.2 to A5.5).

Samples will be handled as regular patient material. The personnel collecting samples and the local diagnostic laboratory are qualified to work with potentially contaminated patient material. The personnel will wear gloves and a protective coat during the sampling.

At the clinical site, 70% ethanol will be used for regular disinfection on surfaces. In case of a spill, the spill will be collected with a tissue soaked in 70% ethanol by personnel wearing gloves, and disposed of in a specific hospital waste container (UN 3291) (see A5.9).

Anti-BCMA transduced T cells, like non-engineered human T cells, do not survive outside of the body and are easily killed; for example, one study demonstrated a CD4 T-cell lifetime of only a few minutes in tap water (Moore 1993).

A4.8. How is the GMO preparation detected after being administered?

Efficacious and long-lasting responses to malignancies treated with CAR T cells likely require robust expansion of the infused CAR T cells, and persistence of functional anti-tumor antigen CAR memory cells in the patient (Frey and Porter 2016).

After administration of KITE-585, the patient's blood will be tested for the presence, expansion, persistence, and immunophenotype of the transduced anti-BCMA CAR T cells. The droplet digital PCR method will be used to quantify the percentage of KITE-585 cells among peripheral blood mononuclear cells and bone marrow mononuclear cells, the number of KITE-585 cells per microliter of blood and number of copies per microgram of cell DNA. Flow cytometry will be used to detect KITE-585 in whole blood, bone marrow, CSF and other tissues, if obtained. A fluorescently-labeled antibody to a short linker sequence in the CAR is used to identify cells that express the CAR transgene.

Waste management

A4.9. Give an overview of the nature and quantity of the waste produced and describe how the waste will be disposed of.

Waste after administration of GMO: Once KITE-585 is administered to the patient, the IV bag along with the IV tubing and any other components that have been in contact with the product before and during administration will be disposed of in bins for specific hospital waste (P621, UN3291) within the patient room. Closed bins will be disinfected from the outside, with 70% ethanol and transported to the logistical exit point of the hospital where the bin(s) are transported to the incinerator.

Patients' *ex vivo* modified T cells, like unmodified T cells, are not shed via saliva, urine, or faeces into the environment, including waste water. No extra precautions are taken.

Waste from sample collection, samples and sample processing waste will be disposed of in bins for specific hospital waste.

Patient room: The patient room consists of a single room with a washroom annexe. Access is restricted to authorized persons. After use, the patient room will be cleaned using standard hospital cleaning and disinfection procedures with for instance 70% ethanol. Any contaminated materials must be disposed of in bins for specific hospital waste (UN 3291).

A5. Environmental risk analysis

Environment-related information originating from earlier experiments

A5.1. Describe the results originating from earlier (pre-) clinical studies with the GMO and which are important for the environmental risk assessment.

Table 8 shows a summary of literature demonstrating that anti-BCMA CAR T- cell products developed by other investigators and used in a variety of clinical and nonclinical settings show no evidence of shedding, recombination, or person-to-person transmission. Preliminary clinical data from 4 ongoing Phase 1 trials in the US of anti-BCMA CAR T-cell products manufactured by other sponsors show response rates ranging from 63% to 94% among 66 efficacy-evaluable patients, and demonstrate acceptable safety profiles. These data support the safety to the environment of this therapy. 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 (KITE-585-501; NCT 03318861).

Table 8. Preliminary Data from Clinical Studies of Anti-BCMA CAR T Cells for Treatment of Relapsed/Refractory Multiple Myeloma

Sponsor/Study (reference)	Transducing Vector	Phase	Patients Dosed	Response		
				ORR (≥ PR) N (%)	≥ VGPR N (%)	CR + sCR N (%)
NCI NCT 02215967 (Brudno et al, 2017)	γ-RVV	1	24	15 (62.5%)	11 (46%)	2 (8%)
Bluebird Bio, Inc. NCT 02658929 (Berdeja et al, 2017)	LVV	1	21 (18 evaluable)	17 (94%)	15 (61%)	10 (56%)
University of Pennsylvania NCT 02546167 (Cohen et al, 2017)	LVV	1	24 (20 evaluable)	11 (55%)	4 (20%)	2 (10%)
Memorial Sloan Kettering Cancer Center (Smith et al, 2017)	γ-RVV	1	6 (4 evaluable by IMWG criteria) [a]	3 (75%)	2 (50%)	0

Abbreviations: CAR, chimeric antigen receptor; CR, complete response; LVV, lentiviral vector; NCI, National Cancer Institute; ORR, objective response rate; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; NCT, National Cancer Trial; PR, partial response; RVV, retroviral vector; sCR, stringent CR; VGPR, very good partial response.

[a] 1 patient treated with baseline M-spike 0.46, thus not evaluable by IMWG criteria, had >50% reduction in M-spike, and normalization of K/L ratio.

Shedding, Transmission of Vector/GMO: Lentiviral vectors are commonly used to transduce cells used in autologous cell-based immunotherapies. A recent review by June and colleagues analyzed 26 trials totaling 460 lentiviral-transduced cell products from 375 subjects (Cornetta et al, 2018). Holzinger and colleagues reviewed 28 clinical trials that used LVVs to generate CAR T-cell products (Holzinger et al, 2016). KITE-585 comprises human T cells modified by an LVV and cannot survive outside the human body. Product release of KITE-585 requires the absence of RCL, and RCL have not been observed to form following infusion of LVV-transduced cells in clinical use (Naldini et al, 2016). There is no evidence of viral shedding of LVVs reported in the literature; further, spreading of LVV to unintended cell types does not occur with clinical-grade LVV in either an in vitro reporter assay or in mice (Cesani et al, 2015). Additional detail regarding the safety features of the LVV delivery system that prevent the formation of RCL are discussed in A2.8 and A2.9.

Latent presence of the vector/GMO: The SIN LVV used to manufacture KITE-585 is removed from the final product during manufacturing and no viral particles or RCL are expected to form following infusion. Thus, there is no latency of the LVV. The modified T cells that comprise KITE-585 will circulate for days, weeks, months, or possibly years in infused patients; this is believed to be a requirement for efficacy. However, the genetically modified T cells comprising KITE-585, like unmodified T cells, do not survive outside the patient.

Possible interaction with other micro-organisms (including viruses): Two gene therapy trials in a combined total of 22 patients with HIV used LVVs to deliver an antisense HIV envelope gene (Levine et al, 2006; Tebas et al, 2013). In up to 6 years of follow-up, no evidence of recombination was observed. This lack of recombination, even in the high-risk setting of a host infected with the

parent virus from which the LVV delivery system is derived, further supports the anticipated safety of lentivirus-transduced human host cells.

Further, clinical trials of the GMO will exclude patients who are known to be acutely or chronically infected with HIV, HCV, HTLV and HBV further reducing the chances of recombination or interaction with other micro-organisms. Patients with any active infection, including viral, will not be administered KITE-585 until the infection has resolved.

Conclusion: Lentiviral vectors have been used to treat many patients in 20 years of clinical use with no evidence of RCL. Further, as detailed above, no reports of RCL have been reported using a lentiviral delivery system. The cells are not pathogenic and do not persist or replicate in the environment. Therefore, no adverse effects on the environment are expected.

Risk analysis

This is the most important aspect of the whole application!

A5.2. State which potentially harmful effects may be linked to exposure of human beings or the environment to the GMO.

Possible adverse effects related to KITE-585: The genetically modified T cells comprising KITE-585 are patient-specific and do not survive outside the patient. The cells are not pathogenic and do not persist or replicate in the environment. Therefore, no adverse effects on the environment, including plants, animals or microbiota, are expected. There is negligible risk of recombination and RCL formation.

In the unlikely event of exposure of anti-BCMA CAR T cells to an unintended human recipient (through accidental injection), the engineered T cells would be rejected by the recipient's innate (ie, complement mediated lysis and phagocytic cells) and adaptive immune systems (Welsh et al, 1975; Welsh et al, 1976; DePolo et al, 2000). Adverse effects would be limited to a normal immune reaction to non-self cells, and no specific adverse effect related to the genetic modification of the cells is expected.

There is a theoretical possibility that the engineered anti-BCMA CAR T cells could persist in the case of unintended transmission to an immunocompromised individual. In this highly unlikely case, graft-versus-host response would be the single most important safety risk. Other theoretical AEs would be the same as the possible AEs in patients, i.e., CRS, neurologic events, cytopenias, infections, and tumor lysis syndrome. Additional details are provided in A2.16.

Possible adverse effects related to free vector particles: KITE-585 comprises CD3-positive T cells that have been transduced with a lentiviral vector which encodes the anti-BCMA CAR. The upstream processing of the incoming apheresis material and ex vivo expansion of genetically modified T cells yield a final product typically containing >99% T cells as assessed by flow cytometry conducted as part of product release testing. The exact composition of KITE-585 final product varies from patient lot to patient lot and may also contain a small percentage (<1%) of autologous NK cells. The culture conditions used to produce the KITE-585 Final Product are not amenable to macrophages, dendritic cells or follicular dendritic cells. Analysis by flow cytometry of KITE-585 samples demonstrates that cells the size and granularity of macrophages or dendritic cells are not detected. However, Kite does not currently monitor for the presence of macrophages, dendritic cells or follicular dendritic cells. Based upon the calculated reduction ratio (see section A2.10), viral vector particles are not expected to remain in KITE-585. Additionally, any potential remaining viral particles would be inactivated by the complement component of human serum.

In the event of accidental injection of KITE-585 final product into unintended recipients, any theoretical remaining infectious viral particles would likely be inactivated by the complement in human serum (DePolo et al, 2000). Even if an infectious particle survived long enough to infect a cell, the vector is SIN and replication deficient; therefore, it could only integrate once, and no further

spreading is possible. No adverse effects would be expected due to a single or very few integration events.

Possible adverse effects related to the theoretical formation of RCL: This is a theoretical concern that has not been observed in the clinic (Holzinger et al, 2016; Naldini et al, 2016; Cornetta et al, 2018). As noted above, KITE-585 uses a SIN vector that is tested for the presence of RCL in both the harvest media and in the end-of-production cells prior to release of each lot. The presence of RCL will be monitored in the clinical study as well. In the highly unlikely event of RCL being present in the KITE-585 final product or formed in the patients, a recombinant virus encoding the CAR transgene could be spread from cell to cell and also potentially to other individuals. In case of such an event, the viral particles would not survive in the environment outside of the body, as described for the parental virus, and in any case, cannot be passed to species other than human and possibly chimpanzee.

A5.3. State according to which scenario the GMO can disperse from the test subject into the environment.

Spread of genetically modified T cells: In the case of accidental release of KITE-585 product, such as through product bag failure or spill, or injury/medical procedure on the patient, the transduced cells cannot persist outside of the patient for long periods or maintain viability in the ambient environment (viability would require appropriate cell culture conditions in the laboratory). Since the cells are sensitive to even moderately harsh conditions, it is highly unlikely that spread would occur in the environment; the genetically modified cells would be quickly rendered nonviable by the prevailing conditions. Therefore, vector spread is very highly unlikely. Safe administration procedures per site guidelines (A4.3) should prevent accidental spills. However, if a spill of KITE-585 occurs, cleanup is according to the site GMO spill procedure (A5.9).

In case of accidental injection to a medical professional or unintended recipient, the immune system of the recipient would eliminate the injected cells. A local reaction or allergic reaction may occur but such reactions are expected to be transient and can be treated with commonly available medications. Thus no lasting negative consequences are expected in the event that an accidental injection occurs.

In summary, the anti-BCMA CAR T cells cannot be a source of further transduction, since the SIN LVV delivery system integrate their genetic content into the T-cell genome without transferring virus-derived coding sequences. Furthermore, the engineered virus is SIN and cannot be mobilized once integrated.

Spread of free viral vector particles: KITE-585 manufacture will occur in the USA; therefore, free virus would be a danger to the EU only if it were present as an impurity in the KITE-585 final product, which is considered highly unlikely given the high reduction ratio and temperature inactivation of LVV particles, as described in A2.10. Furthermore, even if present, free viral particles will be replication-defective and SIN, so they lack the ability to infect more than one cell and therefore spread.

There are no known mechanisms to enable shedding of the LVV, 293FT-K585. This vector is a SIN, HIV-1-based LVV. Once the LVV infects a target cell, the transgene is permanently integrated into the T-cell genome. Further details on the safety features of this vector are provided in A2.8 and A2.9.

Further, autologous T cells transduced with lentiviral particles are not considered true excreta since they, like normal T cells, do not shed spontaneously via saliva, urine, or feces into the environment (Schenk-Braat et al, 2007).

RCL formation during vector manufacture: The 293FT-K585 Vector does not code within its genome any of the elements required for viral growth and replication, which by design renders the LVV replication incompetent. This approach minimizes any potential risk for RCL production since a minimum of four independent recombination events are required for the generation of a functional RCL. RCL has not been detected to date in clinical trials that used similar replication-deficient, SIN LVV delivery systems over 20 years of observation.

The manufacture of 293FT-K585 Vector includes RCL testing of the LVV and the end-of-production cells. The LVV is released only if no RCL is detected.

In conclusion, based on the safety features built into the design of the vector and the release testing performed on KITE-585 prior to shipment to the clinical site, RCL is not contained in the cell product shipped to the clinical site for infusion into patients. Therefore, the GMO is not expected to be infectious and does not pose any risk of deleterious effects to organisms present in the environment.

A5.4. Give an estimate of the chance that the adverse effects described in A5.2 could actually occur.

The likelihood of spread of KITE-585 is negligible because the autologous cell product cannot survive outside patients. Further, free 293FT-K585 vector is removed from the final product, and in any case is replication deficient and could not spread. Since KITE-585 is not shed from the treated subject, there is negligible chance of exposure of the GMO to other persons, irrespective of the total number of subjects enrolled in the KITE-585 clinical trial program. The effect of accidental exposure to KITE-585 through needlestick or transfusion would be negligible in immune-competent individuals, and would be manageable in immune-deficient individuals.

A5.5. Describe the risks that could occur as a consequence of the application of the GMO, taking into account the impact of any risk management measures taken.

The GMO: KITE-585 cells can only survive in the patient from which the cells were derived. Therefore, the GMO does not have the capacity to disseminate vertically or horizontally in the ecosystem.

Accidental injury of the patient and/or loss of blood or blood sampling will not lead to dissemination of the GMO into the environment, as cells will undergo rapid inactivation outside the patient. Dissemination of the GMO could therefore only occur between human beings. However, persons other than the patients from whom the cells have been derived would eliminate the cells as a result of their immune response.

Despite its safety, exposure of people other than the patient being treated with GMO will be avoided by adoption of the following practices:

- Patients will be instructed not to donate blood, organs, tissues or cells for transplantation.
- Following administration of the GMO, materials used will be disposed of in accordance with the institutional requirements for specific hospital waste (UN3291; see A4.9)

Further, personnel who participate in the administration of blood components must be trained in transfusion procedures, and in management of adverse reactions in the patients and safe handling of GMOs.

Safe administration procedures per site guidelines (A4.3) should prevent accidental spills. However, if a spill of KITE-585 occurs, cleanup is according to the site GMO spill procedure (A5.9).

Accidental loss of GMO is unlikely due to controlled procedures of transportation, delivery and use, including all necessary documentation. In the unlikely event of the transmission of GMO to an unintended human recipient, physicians will take all necessary measures to assure safety. Additionally, because KITE-585 cannot survive outside of a human host unless maintained in a cryopreserved state, loss that resulted in exposure of the KITE-585 to ambient temperature would lead to its deactivation.

Free vector particles: The number of free LVV particles in the GMO is expected to be negligible (A2.10). After administration to the patient, any potential remaining viral particles would be inactivated in vivo by the complement component in human blood. Therefore, the vector cannot be transmitted to the environment or other individuals from the patient. Theoretically, if a low number of free LVV particles were present in the GMO, they could enter a medical health care professional by

accidental injection, however this cannot lead to further spreading and is not expected to cause adverse effects (A5.3).

RCL: The risk of formation of RCL is negligible. As part of the patient monitoring, patients are tested for RCL for up to 15 years. In the very unlikely event of RCL detection, the following mitigation will be implemented:

1. Conduct intensive follow-up of the patient in consultation with gene therapy experts, study investigators, and health authorities
2. Inform local and country specific public health officials
3. Identify sexual partners and provide appropriate counseling and intervention

Conclusion: The risks to the environment related to the GMO (KITE-585; anti-BCMA CAR T cells), the possibility of free vector particles and RCL formation is expected to be negligible.

Risk management

A5.6. Which inclusion and exclusion criteria are adopted in the selection of test subjects and what is the effect of these criteria on environmental safety?

Clinical trials of KITE-585 exclude the participation of patients who are known to be infected with HIV, HCV, HTLV and HBV further reducing the chances of recombination with wild-type virus and the generation of RCL. Because of the SIN nature of the LVV, the lack of RCL in the final product, and the negligible likelihood of spontaneous formation of RCL during manufacturing or following infusion, no additional inclusion or exclusion criteria are required in the clinical development program to protect human beings or the environment.

If free LVV particles were somehow to be present as an impurity in a KITE-585 preparation, since the vector is self-inactivating and replication-deficient, the individual vector would need to somehow escape the lymphatic compartment to integrate into a germline cell. This possibility is considered highly improbable.

Maternal leukocytes, including lymphocytes may be present in breast milk. Free LVV particles are not shed from the lymphocytes and in the event of exposure from degraded lymphocytes, the vector is replication deficient. Pregnant and breast-feeding mothers are excluded from clinical trials.

A5.7. Describe which measures are provided for in respect of the hospitalization of the test subject.

KITE-585 is not pathogenic and does not replicate ex vivo, and therefore is not expected to pose a risk to the environment, and hospitalization is not required as a means of protecting against effects of the LVV. However, to monitor subjects for potential adverse effects (A2.16), all subjects will receive treatment with KITE-585 in the hospital and will be observed closely after the infusion. Subjects will remain in the hospital until resolution of all treatment-related toxicity to Grade 1 or lower, or until deemed safe by the study investigator. Thus, subjects treated with KITE-585 will be continuously monitored in a clinical setting in the immediate post-infusion period and will be monitored frequently for safety and efficacy as well as for RCL following discharge. The subjects receive the same standard treatment as patients who are not treated with the GMO product; no additional safety measures are taken in the patient ward.

A5.8. If the test subject is to be hospitalized, what are the criteria for his or her release from hospital?

Subjects should not be discharged from the hospital until permitted by the clinical trial protocol and until discharge is deemed safe by the treating physician. Subjects should remain hospitalized for ongoing KITE-585-related or unexplained fever, hypotension, hypoxia, or ongoing central neurological toxicity > Grade 1, or if deemed necessary by the treating investigator.

A5.9. Describe which measures will be taken to prevent the spread of the GMO to third parties (including medical personnel).

The KITE-585 final product is shipped in a liquid nitrogen dry shipper. Prior to and during administration the GMO is contained; third parties including medical personnel cannot come into direct contact with it.

The administration of KITE-585 will be performed at the UMC Utrecht by experienced health care professionals who are appropriately trained in hygiene procedures and standards regarding the safe storage and handling of human tissues and fluids. As is the case for all standard hospital procedures, the adequate training of personnel for general infection prevention measures, as well as the establishment and maintenance of training records regarding this training, is the responsibility of the UMC Utrecht.

KITE-585 comprises autologous human T cells. Therefore, healthcare professionals should employ universal precautions for the prevention of transmission of blood-borne infections. Established procedures for handling live human cells should be followed per the site guidelines (A4.3) and processes. After KITE-585 is administered to the patient, the IV bag along with the IV tubing and any other components that contain the product will be disposed of as specific hospital waste (A4.9).

All health care professionals involved in the administration will adhere to safe practices to avoid any release of the product into the environment. Health care professionals will wear a protective coat and gloves. Work surfaces and material potentially in contact with KITE-585 will be decontaminated with 70% alcohol, according to facility hygiene procedures.

In case of a spill on the skin, bed, or floor, the site procedure is to collect the spill with a tissue soaked in 70% ethanol, clean the spot with 70% ethanol, and to collect personal protective equipment (coat and gloves) and waste, including contaminated bed sheets, in the specific hospital waste bin. The hands are disinfected with hand alcohol and washed carefully with water and soap. Following handling and administration of KITE-585 to the patient, any unused residual compound remaining in the cryobag and all used materials that have been in contact with KITE-585 such as a protective coat, gloves and tubing will be disposed as specific hospital waste A4.9).

In the event of accidental injection, enhanced bleeding of the wound is advised. The occupational health physician of the hospital should be contacted. Information and reporting on incidents and accidents to regional or national authorities has to be performed according to relevant regulations.

Procedure in case of unexpected situations and serious incidences

A5.10. Describe the procedures to be followed if changes in the risk management are required for medical reasons.

- Prior to and during administration, the GMO (KITE-585) is contained and third parties including medical personnel do not come into direct contact with KITE-585
- Once the product has been infused, third parties including medical personnel cannot come into direct contact with KITE-585, except through accidental needlestick (A5.4).
- KITE-585 is not shed from the treated patient.
- In the event of patient hemorrhage, site personnel will be instructed to use universal precautions and avoid contamination and to follow GMO and site-specific clean-up procedures (A4.9, A5.9).
- In the case of unexpected death of the patient, where an autopsy is required, the involved personnel will be instructed to use universal precautions and avoid contamination and to follow GMO and site-specific clean-up procedures (Siegel et al, 2007).

A5.11. Describe what aftercare will be given if a test subject ends his/her participation in the study prematurely.

Patients have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution. If a patient ends his/her participation in the study prematurely, the planned monitoring for RCL for up to 15 years will be maintained. If a patient is lost to follow-up after receiving KITE-585, no specific measures will be applied, the patients will be monitored according to standard care and applicable international guidelines. If the KITE-585 is not infused, the product will be returned to the manufacturer using the same qualified carriers and methods used for product delivery to the clinical site.

Monitoring

A5.12. Describe how the monitoring will be set up to identify any spread of the GMO.

KITE-585 will not be manufactured in the EU. KITE-585 final product specifications require the absence of RCL. Samples taken for RCL testing at prespecified time points after infusion are shipped to the USA. Since RCL testing is not performed in the Netherlands, RCL testing is excluded from the application.

As KITE-585 is not shed from the test subject (A5.1) no monitoring will be set up to identify spread of KITE-585 outside of the test subject.

The presence, expansion, persistence, and immunophenotype of anti-BCMA CAR T cells will be monitored in the blood of the treated subject primarily by PCR analysis, complemented by flow cytometry (A4.8).

A6. Conclusions of the possible environmental effects

The overall environmental risk of KITE-585 and 293FT-K585 Vector is concluded to be negligible.

In line with the environmental risk assessment and summary notification information format (SNIF) document for the contained use of KITE-585, the following conclusions are in accordance with the considerations and aspects stated in Directive 2001/18/EC Annex II under Point D.1:

1. Likelihood of the GMO to become persistent and invasive in natural habitats under the conditions of the proposed release(s).

There is no likelihood of the GMO (KITE-585) to become persistent and invasive in natural habitats. Contamination with 293FT-KITE585 Vector is expected to be negligible in KITE-585, and these would not pose a threat even if present. Therefore, Kite anticipates no environmental risk associated with the product.

Further, RCL cannot be generated to facilitate person-to-person transfer of the transgene. The lack of documented evidence of development of RCL in clinical trials of T cells transduced with LVVs (Holzinger et al, 2016; Naldini et al, 2016; Cornetta et al, 2018), and a lack of recombination events even in the favorable setting of hosts infected with HIV, from which the LVV delivery system is derived (Levine et al, 2006; Tebas et al, 2013), supports the anticipated safety of lentivirus-transduced human T cells.

2. Any selective advantage or disadvantage conferred to the GMO and the likelihood of this becoming realized under the conditions of the proposed release(s).

There is no selective advantage or disadvantage conferred to T cells genetically modified by lentiviral transduction. Once infused, the transduced T cells are not known or predicted to possess any selective growth advantage in vivo; their half-life is similar to or lower than the nontransduced T cells.

3. Potential for gene transfer to other species under conditions of the proposed release of the GMO and any selective advantage or disadvantage conferred to those species.

There is no known or predicted potential for gene transfer from KITE-585. Administration of KITE-585 is performed within a clinical setting under aseptic conditions. Transmission to other species is improbable. In the event of accidental injection of the autologous medicinal product to an allogeneic, non-target human subject, the cells would be recognized as MHC-mismatched and thus would be cleared by the immune system of the individual.

293FT-K585 Vector is expected to be negligible in KITE-585 due to the high reduction ratio and inactivation at 37° (A2.10). Further, even in unlikely occurrence of contamination by 293FT-K585 Vector, no known or predicted potential exists for gene transfer to non-target organisms.

4. Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO and non-target organisms (if applicable).

Not applicable.

5. Possible immediate and/or delayed effects on human health resulting from potential direct and indirect interactions of the GMO and persons working with, coming into contact with or in the vicinity of the GMO release(s).

Potential immediate and/or delayed effects on the health of persons working with, coming into contact with, or being in the vicinity of either use of KITE-585 or accidental release of 293FT-K585 Vector are not known or predicted.

6. Possible immediate and/or delayed effects on animal health and consequences for the feed/food chain resulting from consumption of the GMO and any product derived from it, if it is intended to be used as animal feed.

Immediate and/or delayed effects on animal health or consequences for the feed/food chain resulting from either accidental consumption of KITE-585 or release of 293FT-K585 Vector are not predicted and have not been observed.

7. Possible immediate and/or delayed effects on biogeochemical processes caused by possible direct or indirect interaction between the GMO and the target and non-target organisms in the vicinity of the GMO introduction(s).

There are no predicted effects on biogeochemical processes by KITE-585.

8. Possible change in the current medical practice.

Regarding a possible change in current medical practice, subjects to be enrolled in the clinical trial(s) of KITE-585 will follow the clinical trial protocols implemented by the investigators at that particular study site. Given the high unmet need in RRMM patients, if the treatment is found to be efficacious, it is likely to alter current medical practice as a treatment for this group of currently underserved patients.

A7. General (personal) information (confidential part)

Responsible employees (RE)

First responsible employee for GMO activities (CP-1)

A7.1. Title, initial, prefix, surname:

A7.2. Institution/company:

A7.3. Department/section:

A7.4. Correspondence address:

A7.5. Postal code and town/city:

A7.6. Telephone and fax number:

A7.7. E-mail address:

Second responsible employee for GMO activities (CP-2, optional)

A7.8. Title, initial, prefix, surname:

A7.9. Institution/company:

A1.10. Department/section:

A7.11. Correspondence address:

A7.12. Postal code and town/city:

A7.13. Telephone and fax number:

A7.14. E-mail address:

Environmental Safety Officer (ESO)

A7.15. Title, initial, prefix, surname:

A7.16. Institution/company:

A7.17. Department/section:

A7.18. Correspondence address:

A7.19. Postal code and town/city:

A7.20. Telephone and fax number:

A7.21. E-mail address:

Signature

On behalf of the legal entity date
Name:

CP-1 date
Name:

CP-2 (if applicable) date
Name:

ESO date
Name:

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Consent form (confidential part)

The undersigned:

Hereby gives his/her consent to the gene therapy office to send on the application forms and the accompanying file to the relevant assessment authorities.

Gives his/her consent to the assessment authorities to use the fully completed file in making its assessment.

Gives his/her consent to the assessment authorities to inform each other and the gene therapy office about the status of the submitted application.

Signed:

Name

Date