ENVIRONMENTAL RISK ASSESSMENT

KITE-585

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LIST OF ABBREVIATIONS

Abbreviation	Definition
BCMA	B-cell maturation antigen
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CMV	Cytomegalovirus
cPPT	Central polypurine tract
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
DLBCL	Diffuse large B cell lymphoma
EU	European Union
G-CSF	Granulocyte colony stimulating factor
GMO	Genetically modified organism
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HSA	Human serum albumin
IV	Intravenous
LTR	Long terminal repeat
LVV	Lentiviral vector
MM	Multiple myeloma
MSCV	Murine stem cell virus
OS	Overall survival
PCR	Polymerase chain reaction
PFS	Progression-free survival
qPCR	Quantitative PCR
RCL	Replication-competent lentivirus
RNA	Ribonucleic acid
RRE	Rev response element
RRMM	Relapsed, refractory multiple myeloma
scFv	Single chain fragment variable
SIN	Self-inactivating
TCR	T-cell receptor
TLS	Tumor lysis syndrome
USA	United States of America
VCN	Vector copy number
VSV-G	Vesicular stomatitis virus glycoprotein
WPRE	Woodchuck post-translational response element

ENVIRONMENTAL RISK ASSESSMENT

1. PRINCIPLES

KITE-585 (referred to hereafter as KITE-585 or as 'the genetically modified organism [GMO]') is an autologous cellular immunotherapy composed of a patient's own T cells engineered to express anti-B-cell maturation antigen (anti-BCMA) chimeric antigen receptors (CARs), in patients with hematologic malignancies in which BCMA is expressed on tumor cells. The environmental risk assessment presented here has been carried out using the results of the nonclinical studies performed to date and in consideration of the following documents:

- Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.
- Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC.
- Council Decision of 3 October 2002 establishing pursuant to Directive 2001/18/EC of the European Parliament and of the Council the summary information format relating to the placing on the market of genetically modified organisms as or in products (2002/812/EC) (Annex I).
- Commission Decision of 24 July 2002 establishing guidance notes supplementing Annex II to Directive 2001/18/EC of the European Parliament and of the Council on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (2002/623/EC).
- EMEA/CHMP/BWP/473191/2006 – Corr. Guideline on environmental risk assessments for medicinal products containing, or consisting of GMOs.
- EMEA/CHMP/GTWP/125491/2006 Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products.

2. OVERVIEW

KITE-585 is a novel, investigational adoptive cellular immunotherapy, composed of engineered T cells containing autologous CARs produced by the ex vivo engineering of a patient's own T cells to allow targeting and killing of tumor cells that express BCMA, a surface protein prevalent on certain hematologic malignancies, including multiple myeloma (MM) and others. Patient-derived T cells are transduced with a lentiviral vector (LVV) encoding the anti-BCMA CAR. It should be noted that the viral transduction of T cells is done outside the European Union (EU). The shipped product does not contain replication-competent lentivirus (RCL).

Many hematologic malignancies have historically had relatively low survival rates, particularly in relapsed/refractory disease. Despite recent treatment advances, 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).

Despite advances in the treatment of relapsed, refractory MM (RRMM), median progression-free survival (PFS) and overall survival (OS) of patients treated with newer therapies remain unsatisfactorily short (6 to 12 months and 1 to 2 years, respectively), reflecting an unmet medical need for more effective therapies (Nooka et al, 2015). These malignancies have in common that they each express BCMA on tumor cells, making them targets for anti-BCMA CAR T cells such as KITE-585. For example, a review of the literature found that 100% of MM cells 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 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). Additionally, a Kite analysis of diffuse large B cell lymphoma (DLBCL) samples in the Cancer Genome Atlas showed clear positivity for BCMA RNA in the majority of DLBCL samples that would likely allow effective targeting of tumor cells with KITE-585. BCMA has also been implicated in 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).

3. GENERAL INFORMATION

3.1. Name and Nomenclature

Recommended International Non-proprietary Name (INN)	Pending
Manufacturer Compound Code:	KITE-585
Name	KITE-585
Abbreviated Chemical Names	Not applicable
Pharmaceutical Form:	Suspension for intravenous injection CAR T cells

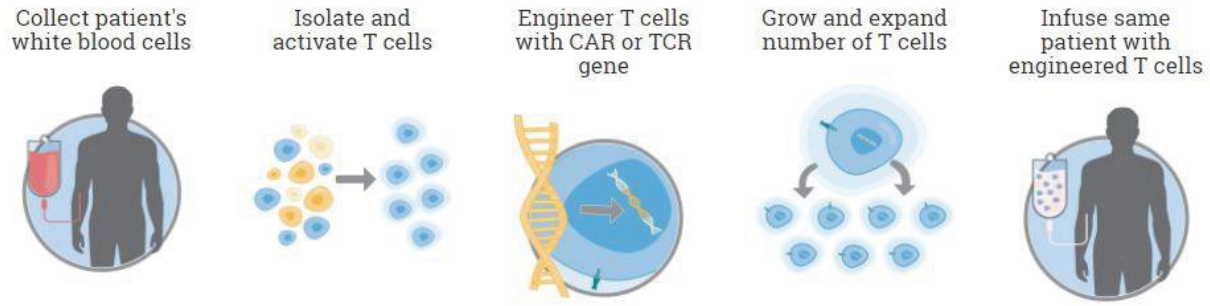
The product consists of a GMO within the meaning of EU Directive 2001/18/EC.

3.2. Background

Engineered autologous cell therapy is a process by which a subject's own T cells are collected and subsequently genetically engineered with a T-cell receptor or a CAR specific for a target antigen expressed on the cell surface of specific malignancies (Johnson et al, 2006; Kochenderfer and Rosenberg 2013; Robbins et al, 2015). These engineered T-cell products represent a promising approach for cancer therapy (Holzinger et al, 2016).

KITE-585 expresses a single chain variable fragment (scFv) that targets the BCMA protein on human plasma cells and BCMA-expressing tumor cells. Engineered autologous cell therapy involves (1) harvesting T cells from the patient's blood, (2) genetically engineering T cells to express cancer-specific receptors, (3) increasing the number of engineered T cells and (4) infusing the functional cancer-specific T cells back into the patient (Figure 1).

Figure 1. The process of engineered Autologous Cell Therapy



Abbreviations: CAR, chimeric antigen receptor; TCR, T cell receptor.

T cells are engineered using a lentiviral vector to express a CAR that recognizes native cancer antigens that are part of intact proteins expressed on the cancer cell surface.

3.2.1. Parental Organism

KITE-585 consists of autologous human T cells. T cells are purified from leukapheresis material, and the T-cell population is then modified *ex vivo* with a lentiviral vector encoding the anti-BCMA CAR.

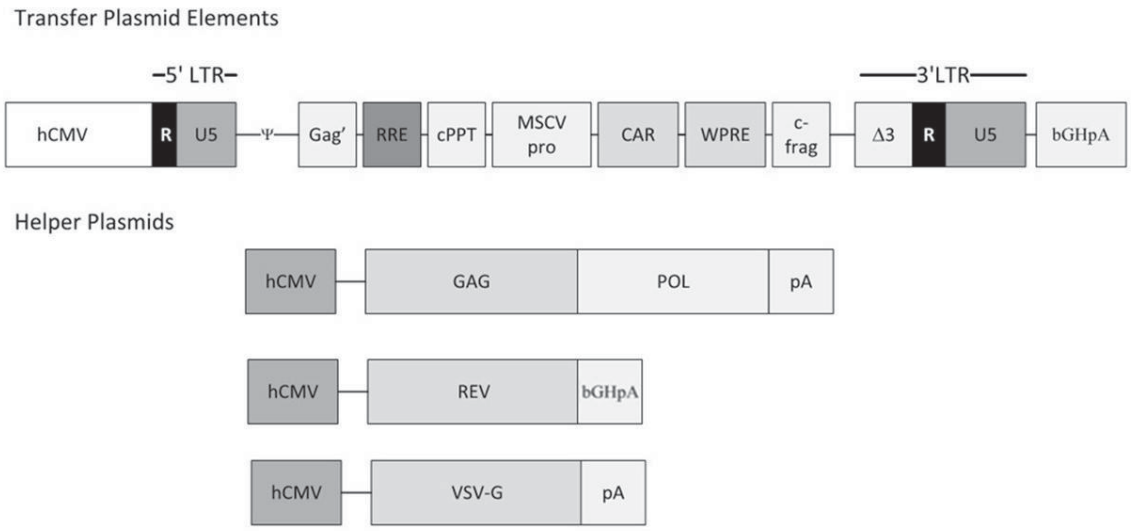
3.2.2. Construct

The lentiviral delivery system used to manufacture KITE-585 is a self-inactivating (SIN) lentiviral vector based on human immunodeficiency 1 (HIV-1). To increase the safety of the lentiviral vector system, essential components are split among four plasmids (a transfer vector plasmid and three helper plasmids). A schematic diagram of the four-plasmid system illustrating the genetic structure of the lentiviral vector 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 Transfer Plasmid: 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 or "helper" plasmids, as described below. 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 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 (bGHpA) terminates expression of the viral genome in the packaging cell line.

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

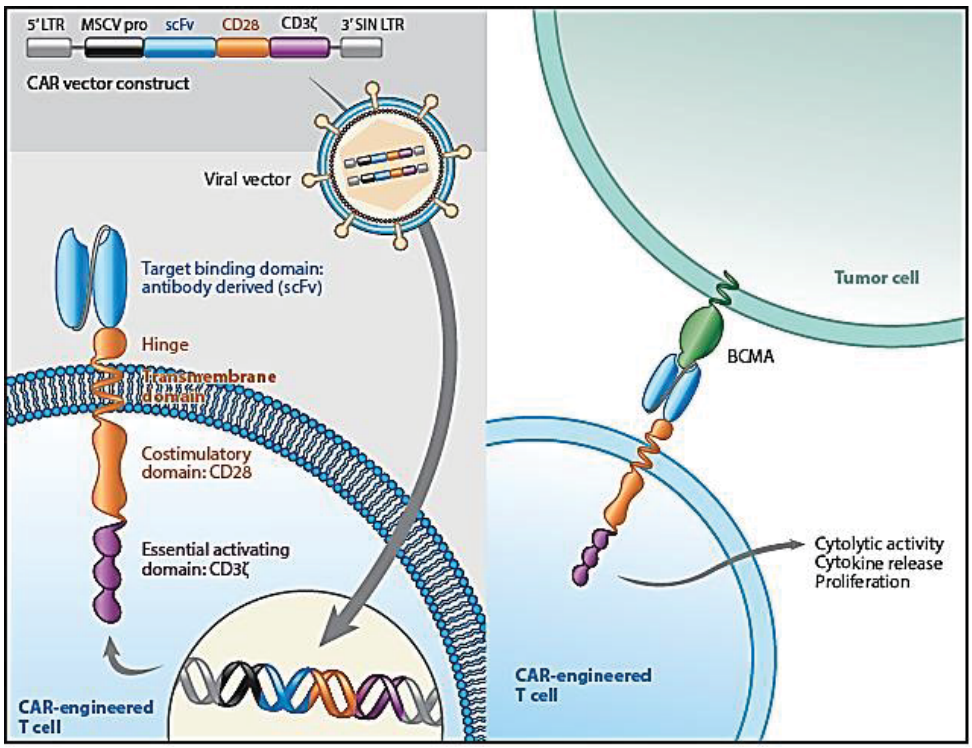


Abbreviations: 3' LTR (Δ3 R U5), a truncated 3'-SIN long terminal repeat containing a deletion of the U3 region to prevent mobilization of the vector; 5' LTR (R U5), a 5' SIN long terminal repeat that exchanges the U3 region for the CMV promoter to drive expression of the RNA viral genome in the packaging cell line; bGHpA, bovine growth hormone polyadenylation; CAR, chimeric antigen receptor; c-frag, unique 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.

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. BCMA functions to promote cell survival 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 DLBCL and HL (Schwaller et al, 2007a; Schwaller et al, 2007b). 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.

Mechanism of Action: A CAR is a fusion protein consisting of an antibody-derived scFv that recognizes a particular extracellular antigen, combined with T-cell activation domains located on the transmembrane and intracellular portion of the molecule (Holzinger et al, 2016). Engagement of the CAR with its target antigen induces T-cell activation, expansion, production of cytokines, and killing of target-expressing cells, in this case BCMA-expressing tumor cells. A schematic of this mechanism is shown in Figure 3.

Figure 3. 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.

3.2.3. Manufacturing

The patients' T cells are collected by leukapheresis at clinical sites and transported at 1°C to 10°C for initial processing using a qualified packaging system. Manufacturing of final product will proceed at Kite Pharma, Inc., (hereafter referred to as 'Kite') located in California, USA. Target T cells are modified at Kite's clinical manufacturing site in compliance with current Good Manufacturing Practices. Key steps in the manufacture of KITE-585 are provided below.

Apheresis processing: Following receipt and inspection of apheresis material, the material is washed using a defined culture wash protocol in a fully automated closed system followed by enrichment of T cells using anti-CD4 and anti-CD8 antibodies conjugated to superparamagnetic iron dextran particles on an automated cell separation system. Enriched CD4 and CD8 positive cells are then cryopreserved and shipped to the US in cryopreservation media containing HSA 2.5%, DMSO 5% and OpTmizer basal medium using a liquid nitrogen vapor-phase dry shipper (a shipper that is built with material that absorbs liquid nitrogen and leaves only the vapor phase) designed to maintain the appropriate storage temperature (≤ -150°C) during transport.

Activation: Cryopreserved T cells are thawed and washed to remove cryopreservation media using a defined culture wash protocol in a fully automated closed system. Cells are then activated in a closed

container containing suitable growth media with soluble anti-CD28 antibody and coated with anti-CD3 antibody.

Lentiviral transduction: LVV particles are added to the activated cells at a multiplicity of infection (MOI) of 5.

Culture wash 1: The T cells are washed twice with fresh culture media under standard aseptic conditions. This step removes the majority of residual LVV and other process related impurities.

T-cell expansion and perfusion: T cells are expanded for up to 7 days under controlled conditions. Starting on Day 4, T cells are fed by semi-continuous perfusion for 3 to 4 days until target dose is achieved. The perfusion method achieves high cell densities ($\geq 3 \times 10^6$ /mL) while maintaining nutrients and eliminating waste metabolites. The semi-continuous perfusion system removes spent media and injects an equal volume of fresh media (2.3 L total from Day 4 to Day 8 of culture), thus serving as an additional LVV removal mechanism.

Culture wash 2 and concentration: The T cells are washed three times in a solution containing 1% human serum albumin (HSA). This step removes residual LVV. The cells are then concentrated to a final volume in preparation for formulation.

Final product formulation: Volume to achieve target dose is calculated based on percent transduction and viable cell concentration of T cells. T cells are formulated in cryopreservation media, transferred to an aluminum cassette and cryopreserved in a controlled rate freezer according to standard protocols.

KITE-585 Final Product is transported to the infusion site by using a liquid nitrogen vapor-phase dry shipper designed to maintain the appropriate storage temperature (≤ -150°C) during transport. KITE-585 final product composition is provided in Table 1.

Table 1. KITE-585 Final Product Composition

Component	Quantity per Unit	Function
Anti-BCMA CAR T cells	Anti-BCMA CAR T cells per dose cohort (± 30%) (Phase 1): • Cohort 1: 3×10^7 • Cohort 2: 1×10^8 • Cohort 3: 3×10^8 • Cohort 4: 1×10^9 De Escalation Dose Cohort • Cohort -1: 1×10^7	Active ingredient
Cryostor® CS10	25 – 34 mL	Cryopreservative
Sodium chloride (0.9%)	20 – 27.2 mL	Tonicity
Human serum albumin (25%)	5 – 6.8 mL	Stabilizer

Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor.

3.3. Information relating to the Conditions of Release and the Receiving Environment

3.3.1. Transport and Storage

KITE-585 (the GMO, consisting of autologous T cells that have been transduced *ex vivo* and do not contain RCL) is cryopreserved and transported in a liquid nitrogen dry shipper back to the site of the EU qualified person (QP), who will release the product. The product will then be transported to one of the participating sites according to good distribution practice (GDP).

3.3.2. Information on the Release

The release is limited to patients in the clinical trial program for KITE-585. KITE-585 will be administered intravenously to patients with hematologic malignancies that are known to express BCMA on tumor cells, with a single-use delivery system. The intended release is limited to participating pre-specified centers. The number of patients to be treated is restricted by the clinical study protocol.

3.3.3. Handling and Administration

KITE-585 is supplied cryopreserved in cryostorage bags. The cryostorage bags containing KITE-585 arrive frozen in the vapor phase of a liquid nitrogen dry shipper. 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.

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 (eg, site number, patient ID number) is essential. Prior to administration of KITE-585, the product label will be checked by two personnel at the research site. The personnel will be asked to complete the Kite Countersignature Form.

The volume of KITE-585 infused, the thaw start/stop time, and KITE-585 administration start/stop time, will all be noted in the patient medical record. The product must not be thawed until the patient is ready for the infusion.

KITE-585 is administered on Day 0, after optional bridging therapy and the last dose of non-myeloablative conditioning chemotherapy (fludarabine and cyclophosphamide) treatment.

KITE-585 will be infused 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.

Research sites will take the necessary steps to ensure all premedication, thawing and completion of KITE-585 infusion are completed within 1 hour.

Trained study staff will administer KITE-585 intravenously using standard medical precautions for immunosuppressed patients. Protective isolation will be as per the institutional standards and policies. Even though KITE-585 is not pathogenic and does not replicate, deliberate 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 any additional procedures per institutional guidelines for cell and gene therapy. No extra safety measures will be taken for KITE-585.

3.3.4. Measures in Case of Unintended Release or Misuse

The modified T cells comprising KITE-585 are patient-specific and, once thawed, 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 are expected. At site, 70% ethanol will be used for regular disinfection of surfaces, or per institutional guidelines. In case of a spill, the surface will be treated with 70% ethanol, 1000 ppm chloride, or other disinfectant per institutional guidelines, and contaminated waste collected in appropriate GMO hospital waste containers.

In the unlikely event of anti-BCMA CAR T cells being administered to an unintended human recipient (through accidental injection or misuse), the engineered T cells would be rejected, and eliminated through the individual's innate (i.e. complement-mediated lysis and phagocytic cells) and adaptive immune system (Welsh et al, 1975; Welsh et al, 1976; DePolo et al, 2000). In this highly unlikely case, graft-versus-host response would be the single most important safety risk. 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.

3.3.5. Shedding

Shedding of the vector is not anticipated. The vector used in KITE-585 production is replication incompetent. There is no evidence of viral shedding of lentiviral vectors 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). 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 (Holzinger et al, 2016; Naldini et al, 2016; Cornetta et al, 2018). 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).

3.3.6. Genotoxicity and Carcinogenicity

The theoretical potential exists to generate RCL during vector manufacturing via recombination of the different viral components; 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). In this unlikely scenario, the RCL could potentially

infect new cells and increase the chance of insertional mutagenesis. The safety features of the viral vector that prevent the formation of RCL are discussed further in Section 3.2.2. The presence of RCL will be monitored in the clinical study.

KITE-585 comprises autologous T cells. There is no carcinogenicity concern for humans or for other animal species from KITE-585. However, there exists a theoretical concern that transduction of autologous cells with lentiviral vectors may give rise to gene disruption caused by the integration of viral DNA into cellular DNA that could result in insertional oncogenesis in affected cells in the patient being treated (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; no case of malignancy has been reported to date for patients treated with LVVs (Levine et al, 2006; Cartier et al, 2009; Cavazzana-Calvo et al, 2010; Aiuti et al, 2013). To minimize possible insertional mutagenesis, a limit of 5 or fewer copies of vector (VCN) per cell is implemented for final product release of KITE-585. Patients will be monitored for these events as part of clinical study follow-up.

3.4. Information Relating to the Interactions between the GMO and the Environment

The characteristics of the GMO, KITE-585, that affect survival, multiplication and dissemination are detailed below in Table 2. Although KITE-585 final product release requires an absence of RCL, and it has been documented in the literature that clinical-grade LVV does not appear to spread in vivo (Cesani et al, 2015), where appropriate, discussion regarding the unlikely event of LVV contamination of final product is included in Table 2.

Table 2. Characteristics of KITE-585 Affecting Survival, Multiplication and Dissemination

Characteristics	KITE-585 Compared with Endogenous T Cells
Fitness, stability, resistance to inactivation	The survival of human blood cells requires a complex combination of special media, temperature and CO_2. The environmental conditions outside the host (body) are substantially different and not appropriate for human blood cell survival (temperature, pH, UV and a change in the biophysical and biochemical conditions). T cells are considered fragile cells that do not survive outside of the body; for example, one study demonstrated a CD4 lifetime of only a few minutes in tap water (Moore 1993). Product release of KITE-585 requires the absence of RCL. However, if free lentiviral particles were somehow to be present as an impurity in a KITE-585 preparation, they would be quickly inactivated upon infusion by human complement (DePolo et al, 2000) and since the potential for recombination or mobilization is limited to humans (Kallings 2008; King et al, 2013) there would be no transmission to the environment possible.
Reversion to wild-type,	The GMO comprises human T cells engineered to express a CAR gene inserted into the genome via lentiviral transduction. If free lentiviral particles were somehow to be

Characteristics	KITE-585 Compared with Endogenous T Cells
regain of replication-competency or virulence	present as an impurity in a KITE-585 preparation, they would be quickly inactivated upon infusion by human complement (DePolo et al, 2000). Furthermore, the LVV delivery system used in production of KITE-585 is replication-defective. To create a safe vector delivery system, 6 of 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. The genes *gag-pol* and *rev* are encoded on separate helper plasmids to produce a replication-deficient LVV delivery system. The vector is also SIN because of deletions in the U3 region of both the 5' and 3' LTRs, such that the ability to produce viral RNA from the viral LTR promoter is removed; thus, necessary elements for generating replication-competent viruses are eliminated. Together, the absence of the HIV-1 accessory genes, coupled with removal of transcriptional elements in the 5' and 3' LTR render the vector replication-incompetent. These alterations to the original vector make it highly improbable that RCL would be generated. In support of the safety of the lentiviral vector system used in KITE-585, no evidence has been observed of RCL in HIV-derived lentiviral vectors (Holzinger et al, 2016; Naldini et al, 2016; Cornetta et al, 2018).
Competition with existing species	The GMO, which comprises endogenous patient T cells engineered to express a single transgene, is not predicted to compete with endogenous T cells in the patient. T cells cannot survive outside humans (Moore 1993), so competition with existing species is not applicable. If free lentiviral particles were somehow to be present as an impurity in a KITE-585 preparation, lentiviral particles could not compete with wild-type HIV-1; they are replication deficient and are missing approximately 85% of the wild-type HIV genome. Recombination of the LVV with wild-type HIV virus in a human host cell has not been observed even in the presence of gene therapy trials in HIV-infected individuals (Levine et al, 2006; Tebas et al, 2013), thus is not anticipated. KITE-585 is not intended to be disseminated and thus no competition is expected outside the treated patients.
Potential to remain latent	CAR T cells persist for weeks to months (Frey and Porter 2016). Because the provirus is an integrated part of the host genome, provirus genetic material would persist as long as CAR T cells continue to be detected in patients. However, because the vector is replication incompetent, there is no risk of a reactivation of virus that could lead to infection of other cells in the patient or shedding of lentiviral vector. If free lentiviral particles were somehow to be present as an impurity in a KITE-585 preparation, any potential remaining viral particles would be inactivated by the complement component of human serum.

Characteristics	KITE-585 Compared with Endogenous T Cells
Traits providing selective advantage	Compared with endogenous T cells, KITE-585 cells are not anticipated to have a selective advantage in the host. Like all T cells, KITE-585 cells will expand in the presence of antigen, in this case, BCMA-expressing tumor cells; and like all T cells, most of these expanded T cells will undergo apoptosis after BCMA antigen disappears (Lenardo et al, 1999). A case report found an elimination half-life of anti-CD19 CAR T cells of 31 days (Porter et al, 2011), and a doubling time of 1.2 days, similar to that for endogenous T cells (Macallan et al, 2004). If free lentiviral particles were somehow to be present as an impurity in a KITE-585 preparation, they would not compete with wild-type HIV-1, nor recombine with HIV-1. Further, the permissive cell line used for production of vector (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.
Harmful inserts	KITE-585 contains no harmful inserts. The following genetic elements are ultimately incorporated to CAR T cells. These are illustrated in Figure 2. Murine stem cell virus (MSCV) promoter derived from the Moloney murine leukemia virus LTR drives the expression of the anti-BCMA CAR. In addition, a WPRE sequence, derived from Woodchuck hepatitis virus, was added downstream to the CAR to improve stability, expression of the construct, and minimize read-through of the promoter. The anti-BCMA CAR transgene recognizes and binds tightly to the BCMA antigen on MM cells, targeting these cells for killing by the engineered CAR T cells. The vector genome also contains the following lentiviral elements that are incorporated to the host genome: • LTRs contain repeat sequences at the extreme ends of the RNA required for reverse transcription, and target recognition sites for integration. The LTRs have been modified to be replication-deficient: the U3 regions of both the 5' and 3' LTRs have been completely or almost completely deleted. • The packaging signal, Ψ, overlaps the 5' LTR and a small portion of the gag gene. This is an RNA structural feature required for incorporation of the viral RNA genome within particles, in this case of the 293FT packaging cells. • The RRE is a sequence to which the Rev protein binds and exports transcribed viral RNA from the nucleus into the cytoplasm of the packaging cells • The cPPT is a region towards the 3' end of the genome that promotes the transportation of the viral genome into the nucleus of non-dividing cells. The CAR transgene is composed of the following elements, listed in order: • N-terminal signal peptide from human CD8α: the signal peptide for cell-surface CD8α directs the CAR transgene to the surface of T cells

Characteristics	KITE-585 Compared with Endogenous T Cells
	• The CAR transgene is a fully human scFv derived from human monoclonal antibody RD-1 using an 18-residue linker to join heavy and light variable domains • A human truncated CD28 spacer containing hinge, transmembrane, and intracellular signaling domains: CD28 is a T-cell specific cell surface glycoprotein • Human CD3ζ cytoplasmic activation domain: a T-cell receptor (TCR)-associated activation domain. There are no vector elements for which the origin or function is unknown. **Elements of the vector that are not incorporated to the GMO:** LVV elements not incorporated into the GMO are the CMV promoter used to transcribe the vector genome in 293FT cells during production of the LVV and elements of the packaging plasmids (*gag-pol, env,* and *rev* elements).
Transcriptional control systems	The LVV is SIN due to substantial modification of the 5' and 3' LTRs from HIV-1. The U3 region of the 5' LTR is completely deleted for safety, and the 3' LTR is substantially truncated. The vector is replication defective, and does not propagate in the human T cells that are transduced with this viral vector. Also, an MSCV promoter is present in KITE-585 to drive expression of the CAR transgene. A WPRE element is also present. The WPRE is a sequence derived from woodchuck hepatitis virus that improves stability and expression of the CAR transgene, while minimizing read-through of the promoter.
Horizontal gene transfer	Horizontal gene transfer is a naturally occurring process in the environment and is crucial for the microbial diversity in the environment. Any type of DNA, including KITE-585 genomic DNA and its constituents, could theoretically be taken up by microorganisms as nutrition and in rare cases can be integrated into the microbial genome. However, KITE-585 is not to be disseminated into the environment, and KITE-585 does not contain any bacterial promoters which would allow expression of the transgene in such organisms. KITE-585 does not contain any function which would specifically confer a selective advantage or disadvantage to microorganisms.
Product impurities	KITE-585 comprises $CD3^+$ T cells that have been transduced with an LVV encoding an anti-BCMA CAR. The upstream processing of the incoming apheresis material and ex vivo expansion of genetically modified T cells yield a final product which is typically composed of > 99% T-cells as assessed by flow cytometry 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

Characteristics	KITE-585 Compared with Endogenous T Cells
	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, 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. Every batch of KITE-585 is thoroughly tested and meets the quality standards for medicinal products. Release specifications require sterility and absence of mycoplasma by quantitative polymerase chain reaction (qPCR), gram stain, endotoxin levels below specific limits, and absence of RCL by qPCR. Specific primers designed to amplify the VSV-G envelope gene and *gag-pol* polygene are used to detect the presence of RCL sequences. Product release of KITE-585 also requires the absence of RCL.

Abbreviations: CAR, chimeric antigen receptor; CD, cluster of differentiation; CMV, cytomegalovirus; cPPT, central polypurine tract; gag-pol, lentiviral group specific antigen (gag) and polymerase (pol) polyproteins; GMO, genetically modified organism; LTR, long terminal repeat; LVV, lentiviral vector; MSCV, murine stem cell virus; qPCR, quantitative polymerase chain reaction; RCL, recombination competent lentivirus; RRE, Rev response element; SIN, self-inactivating; UV, ultraviolet; VSV-G, Vesicular stomatitis virus glycoprotein; WPRE, Woodchuck posttranslational response element.

The possible interactions of KITE-585 with the environment are detailed in Table 3. KITE-585 is not disseminated into the environment. It is administered intravenously to subjects, with procedures to minimize exposure to healthcare personnel, and to contain environmental exposure using standard hospital protocols for disposal of the cryopreservation bag containing the GMO, infusion tubing and other materials that have been in contact with the product before administration to the patient will be disposed in accordance with site guidelines for GMO waste.

Table 3. Interaction of KITE-585 with the Environment

Interaction	Exposed Environment (Waste Water)	Exposed People (Healthcare Personnel, Third Parties), (Pet) Animals
Stability, resistance to inactivation	KITE-585 is predicted to have no additional stability or resistance to inactivation in comparison with unmodified human T cells. KITE-585 cells do not survive outside the patient. In the case of accidental release of KITE-585 product, the transduced cells cannot persist outside of the patient for	In the unlikely event of anti-BCMA CAR T cells being accidentally administered to an unintended human recipient, the engineered T cells would be rejected, and eliminated through the individual's innate (i.e. complement-mediated lysis and phagocytic cells) and adaptive immune system (Welsh et al,

Interaction	Exposed Environment (Waste Water)	Exposed People (Healthcare Personnel, Third Parties), (Pet) Animals
	long periods and maintain viability in the ambient environment (except for in 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 non-viable by the prevailing conditions. Further, patients' *ex vivo* modified T cells are not shed via saliva, urine, or faeces into the environment, including waste water. Product release of KITE-585 requires the absence of RCL. However, it can be noted that both wild-type, infectious HIV-1 particles and human T cells are rapidly killed in dechlorinated tap water, representative of conditions of waste water (Moore 1993) so exposure to waste water of either LVV particles or KITE-585 is predicted to have no effect on the environment.	1975; Welsh et al, 1976; DePolo et al, 2000). In this highly unlikely case, graft-versus-host response would be the single most important safety risk. 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 no risk of transmission of HIV, HBV or HCV because subjects are excluded from study participation if they harbor these infections. There is a theoretical possibility that the engineered anti-BCMA CAR T cells could persist if transmitted 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 information on side effects is provided in Table 6. There would not be an anticipated enhanced stability of KITE-585 compared with unmodified T cells. Since there would be no significant amount of BCMA antigen present except in the late B cell lineage where it is endogenously expressed, KITE-585 could potentially eliminate endogenous BCMA-expressing mature B cells and plasma cells. KITE-585 cells would then be subject to elimination after the disappearance of BCMA antigen as occurs with mature T cells in the absence of antigen (Lenardo et al, 1999).

Interaction	Exposed Environment (Waste Water)	Exposed People (Healthcare Personnel, Third Parties), (Pet) Animals
Reversion to wild type, regain of replication-competency or virulence	As described in Table 2, LVV particles cannot regain virulence due to multiple safety mechanisms and reversion to wild type has never been observed in 20 years of clinical use of LVVs; further, neither T cells nor viral particles survive in waste water (Moore 1993).	Even in the presence of active HIV infection, there is no evidence of recombination between wild-type virus and HIV-1-based LVV delivery systems. Two gene therapy trials in patients with HIV used lentiviral vectors to deliver an antisense HIV envelope gene (Levine et al, 2006; Tebas et al, 2013). A lack of recombination even in the highly favorable setting of hosts infected with the parent virus from which the LVV delivery system is derived, further supports the anticipated safety of lentivirus-transduced human host cells.
Competition with existing species, interaction with GMOs.	As described in Table 2, KITE-585 is not intended to be disseminated into the environment. KITE-585 comprises human T cells, which cannot survive outside the human body so they are not predicted to have an effect on the environment. If free LVV were present, viral particles are predicted to be incapable of survival in wastewater (Moore 1993) so competition is not predicted.	KITE-585, which comprises endogenous patient T cells engineered to express a single transgene, is not predicted to compete with endogenous T cells in the patient, except in the normal antigen-dependent manner of all T cells, as described in Table 2.
Potential to remain latent	Human T cells, T cells infected with HIV, and free HIV cannot survive in wastewater (Moore 1993). Given that even wild-type HIV-1 cannot survive in human wastewater, LVV is predicted not to be capable of survival in wastewater (Moore 1993). Given the very low likelihood of survival in wastewater, neither KITE-585 nor the very unlikely potential contaminant LVV is predicted to survive sufficiently long to encounter a possible host, the only two natural hosts for the wild-type virus.	Human T cells cannot survive outside the patient's body. Therefore, no opportunity exists to transduce a suitable host cell, if hypothetically exposed to healthcare personnel, third parties or animals. In the unlikely event of the provision of anti-BCMA CAR T cells to an unintended human recipient (through accidental injection), the engineered T cells would be rejected, and eliminated through the individual's innate (ie,

Interaction	Exposed Environment (Waste Water)	Exposed People (Healthcare Personnel, Third Parties), (Pet) Animals
		complement mediated lysis and phagocytic cells) and adaptive immune system (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 would be expected.
Traits providing selective advantage	Human T cells cannot survive in wastewater (Moore 1993). There are no antibiotic resistance sequences in the provirus. The transgene and regulatory sequences (RRE, WPRE, MSCV promotor) in the provirus (Figure 2) contain no sequences that are known to be used by microorganisms in the environment. The CAR transgene recognizes and binds a human protein, BCMA, which would not confer a selective advantage even if it could be taken up by microbes.	KITE-585, which comprises endogenous patient T cells engineered to express a single transgene, has no known selective advantage over endogenous T cells, except presumably for the well-documented processes of adaptive immunity in which T cells expand in the presence of antigen (Janssen et al, 2003).
Harmful inserts	KITE-585 does not contain harmful inserts. (Table 2). The CAR transgene is expressed in modified patient T cells and would have no effect on the environment, as it is very specific to BCMA, a human protein. KITE-585 cannot survive in wastewater.	KITE-585 does not contain harmful inserts, and cannot survive outside the patient.
Horizontal gene transfer	As described in Table 2, horizontal gene Transfer is a naturally occurring process in the environment and is crucial for the microbial diversity in the environment. KITE-585 cannot survive in the environment, but it also does not contain any function which would specifically confer a selective advantage or disadvantage to microorganisms in	KITE-585 cannot survive in the environment, and horizontal gene Transfer has not been documented to occur between mammalian cells, in any case. If free LVV particles were somehow to be present as an impurity in a KITE-585 preparation, host cell genome integration is, in theory,

Interaction	Exposed Environment (Waste Water)	Exposed People (Healthcare Personnel, Third Parties), (Pet) Animals
	wastewater.	possible, although very unlikely, in persons exposed. However, virucidal solutions are used in case of accidental spill in the clinic (Palesch et al, 2014). Further, personnel handling product bags containing KITE-585 will follow the appropriate precautions, including universal precautions for body fluids (Siegel et al, 2007) and any additional procedures per institutional guidelines for cell and gene therapy.
Vertical gene transfer	Not applicable.	Germline: KITE-585 comprises genetically modified, differentiated T cells, and does not shed, as discussed in Table 2. Germline transmission would require that the transgene be integrated into germline cells, which would require the presence of LVV. 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. Breast milk: 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.
Product impurities	As described in Table 2, every batch of KITE-585 is thoroughly tested and has very low levels of impurities, as required	Each batch of KITE-585 is quality tested and meets quality standards for medicinal products. No evidence from

Interaction	Exposed Environment (Waste Water)	Exposed People (Healthcare Personnel, Third Parties), (Pet) Animals
	for medicinal products. Negligible levels of impurities will be released in wastewater.	early results of clinical trials indicates that either CAR T cells or KITE-585 impurities cause harmful effects. Unintended exposure of contact persons is therefore not predicted to result in harmful effects.

Abbreviations: AE, adverse event; BCMA, B cell maturation antigen; CRS, cytokine release syndrome; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LVV, lentiviral vector; MSCV, murine stem cell virus; RCL, replication-competent lentivirus; RRE, rev response element; WPRE, woodchuck posttranslational response element.

3.4.1. Monitoring Techniques

KITE-585 Final Product RCL testing: KITE-585 final product specifications require the absence of RCL, and in any case KITE-585 is not manufactured in the EU. Testing 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). Any potential RCL in KITE-585 will be detected by an RCL by qPCR method.

The RCL by qPCR method tests 200 ng DNA per replicate, with a sensitivity of 10 VSV-G or *gag-pol* genome copies per replicate. The statistical derivation confirms that this is sufficient DNA and sensitivity to detect an RCL event with 95% confidence.

Patient Monitoring: As KITE-585 is not shed from the test subject, 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.

The presence of RCL in the blood of treated patients will also be monitored for 15 years. Samples taken for RCL testing at prespecified time points after infusion are shipped to the USA. Therefore RCL testing is not performed in the EU, RCL testing is excluded from the application.

3.4.2. Potential Adverse Effects to Animals, Plants or Populations in the Environment

Potential effects to animals and plants are listed in Table 4 and potential adverse effects on populations in the environment are detailed in Table 5.

Table 4. Potential Adverse Effects to Animals and Plants

Characteristics	Effects to Exposed Animals and Plants
Toxic/ tumorigenic/ oncogenic	KITE-585 comprises patients' own T cells containing an integrated CAR transgene delivered by an LVV. If exposed to animals, it is inconceivable how the human T cells, which do not survive outside of the human body, could enter and harm an animal. LTR retrotransposons with structures that are identical to those found in simple vertebrate retroviruses, including a putative env gene, have been discovered in plants. However, LVV and HIV-1 are not plant retroviruses and there is only very limited literature available regarding the potential existence of retroviruses in plants. Since HIV-1 and LVV have a narrow tropism, confined to humans and chimpanzees, any adverse effects in plants are considered extremely unlikely.

Table 5. Potential adverse effects to populations in the environment

Characteristics	Adverse Effect(s)
Horizontal gene transfer	KITE-585 is not predicted to compete with endogenous T cells in the patient. T cells cannot survive outside humans; for example, a study demonstrated a CD4 T cell lifetime of only a few minutes in tap water (Moore 1993). Shedding is the only theoretical manner in which LVV could enter the environment via waste water. Shedding of the vector is not anticipated. There is no evidence of viral shedding reported in the literature in 20 years of clinical experience with HIV-derived lentiviral vectors (Holzinger et al, 2016; Naldini et al, 2016; Cornetta et al, 2018); also, 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). Therefore, it is concluded that there is extremely low probability of horizontal gene transfer.
Altered susceptibility to pathogens	No evidence exists that KITE-585 will alter the susceptibility to pathogens in facilitating the dissemination of infectious diseases and/or creating new reservoirs or vectors. The components of the LVV lack any potentially pathogenic sequences (Figure 2) which could be transferred to microorganisms and, thus, confer a pathogenic potential to otherwise non-pathogenic microorganisms.
Compromising prophylactic or therapeutic medical, veterinary, or plant protection	KITE-585 is not anticipated to compromise prophylactic or therapeutic medical veterinary or plant protection treatment since it contains no sequences that could interfere with the prophylaxis or treatment of pathogenic microorganisms, ie, it contains no antibiotic resistance genes.

Characteristics	Adverse Effect(s)
treatments	
Effects on biogeochemistry, through changes in soil decomposition of organic material	The genetically modified T cells that comprise KITE-585 cannot survive outside of the body. Since the LVV is self-inactivating and replication-defective, the proliferation of the LVV is not possible. Therefore KITE-585 and the LVV are not expected to have any effect on biogeochemistry since they do not have the potential to proliferate and disseminate in the environment.

Abbreviations: CAR, chimeric antigen receptor; HIV, human immunodeficiency virus; LTR, long terminal repeat; LVV, lentiviral vector.

3.5. Evaluation of the Potential Consequences and Likelihood of Each Adverse Effect

Potential or theoretical adverse effects are listed in Table 6 below and the predicted magnitude of each potential consequence has been assessed based on severity of the theoretical AE. The estimated likelihood of such an AE actually occurring is detailed in Table 7 below. The overall risk of the GMO has been evaluated by weighing the potential severity with the likelihood, detailed in Table 8.

Table 6. Potential Consequences of Adverse Effects of KITE-585 to People and the Environment

Adverse Effect	Potential Consequence	Magnitude (Severity)
Toxic effects to humans	There are no predicted toxic effects to humans other than the intended recipient since human complement eliminates non-self cells efficiently. 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, and eliminated through the individual's innate (i.e. complement mediated lysis and phagocytic cells) and adaptive immune system system (Welsh et al, 1975; Welsh et al, 1976; DePolo et al, 2000). Graft-versus-host response would be the single most important safety risk. 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. The following adverse events (AE) are considered important potential risks with KITE-585 for patients: CRS, neurologic events, cytopenias, infections, and tumor lysis syndrome. It should be noted that these potential risks are on-target, on-mechanism effects	Potentially severe in treated patients, but negligible toxicity in inadvertently exposed healthcare personnel or other exposed persons, since their immune systems would destroy KITE-585 due to tissue mismatch and rejection.

Adverse Effect	Potential Consequence	Magnitude (Severity)
	that are known to be associated with CAR T cell therapy (Shank et al, 2017). These AEs are related to the anti-tumor activity of the CAR T cells, and not related to the genetic modifications needed to create the CAR T cell, per se. Further description of each AE is provided below: **CRS.** CRS is a symptom complex associated with the use of monoclonal antibodies and immune activating therapies that results from the widespread activation of both immune and non-immune cell types. CRS has been observed in human patients treated with anti-BCMA CAR T cells (Ali et al, 2016; Berdeja et al, 2017; Cohen et al, 2017). 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. Clinical manifestations commonly include fever, hypotension, tachycardia and hypoxia. More severe symptoms may include clinical heart failure, vascular leak syndrome, acute renal failure, and other organ dysfunction (Lee et al, 2014). There have been reports that some of the severe CRS symptoms respond rapidly to infusion of an IL-6 receptor antagonist such as tocilizumab (Davila et al, 2014; Lee et al, 2014). Tocilizumab use can be considered as per standard-of-care. **Neurotoxicity**. Neurologic events (eg, encephalopathy, cerebral edema, somnolence, aphasia) have been observed with anti-CD19 T-cell therapies including blinatumomab and CAR T-cell therapies. Early reports with anti-BCMA CAR T cells have detailed neurologic events as well (Ali et al, 2016; Cohen et al, 2016). Tocilizumab, when symptoms of CRS accompany neurologic events, and corticosteroids in the absence of CRS should be used to manage neurologic events per standard-of-care. **Cytopenias and Neutropenic Fever.** The conditioning chemotherapy regimen (fludarabine +	

Adverse Effect	Potential Consequence	Magnitude (Severity)
	cyclophosphamide) is expected to cause bone marrow suppression. Furthermore, many patients with RRMM have high marrow-burden disease and have received numerous prior myelosuppresive therapies, each of which may impact peripheral blood counts. Most patients are anticipated to experience this AE. Infection prevention with prophylactic broad spectrum antibiotics per established clinical guidelines and institutional standard of care. Granulocyte colony-stimulating factor (G-CSF) is used to manage according to published guidelines (eg, Infectious Disease Society of America). Neutropenic fever should also be treated with empiric antibiotics and other supportive measures per established clinical guidelines (Klastersky et al, 2016). **Infections.** Due to the conditioning chemotherapy regimen, this is an important risk. Prophylaxis is recommended. Evaluation for a source of infection should be performed per institutional guidelines. Corticosteroids should be avoided. **Tumor Lysis Syndrome.** All subjects with significant malignancy burden are at possible risk of developing tumor lysis syndrome. Prophylactic treatment (eg, allopurinol) is advised per institutional guidelines prior to initiation of conditioning chemotherapy.	
Pathogenicity to humans	KITE-585 is a cellular therapy and is not pathogenic. LVV is not shed from KITE-585. There is no evidence of viral shedding reported in the literature in 20 years of clinical experience with HIV-derived lentiviral vectors for gene therapy (Holzinger et al, 2016; Naldini et al, 2016; Cornetta et al, 2018); also, 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).	Negligible

Adverse Effect	Potential Consequence	Magnitude (Severity)
Tumorigenicity to humans	Theoretical risks, never observed in humans, include secondary malignancy and generation of RCL: **Secondary malignancy.** There exists a theoretical concern that transduction of autologous cells with lentiviral vectors 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 oncogenesis were reported in 12 immunodeficient patients treated with retrovirally-transduced hematopoietic stem cells. No case of malignancy has been reported to date for patients treated with lentiviral vectors (Levine et al, 2006; Cartier et al, 2009; Cavazzana-Calvo et al, 2010; Aiuti et al, 2013). Additionally, cells that are terminally differentiated such as T cells are considered more resistant to transformation than the stem cells in which secondary malignancies were observed with the use of retroviruses (Cattoglio et al, 2010). To minimize possible insertional mutagenesis, a VCN limit of 5 or fewer per cell is implemented for final product release of KITE-585. Should insertional oncogenesis occur, standard-of-care treatments would be administered for the particular secondary malignancy observed. **Replication-competent lentivirus.** The potential exists to generate RCL during vector manufacturing via recombination of the different viral components. If such an event were to occur and if infused into the patient, the RCL could potentially infect new cells and increase the chance of insertional mutagenesis. 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). KITE-585 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.	Potentially severe in the patient, not possible in exposed healthcare personnel or other exposed persons; however, this has never been observed in 20 years of clinical use with LVVs.

Adverse Effect	Potential Consequence	Magnitude (Severity)
Germ line transmission in humans	As discussed in Table 3, vertical gene transfer, KITE-585 comprises genetically modified, differentiated T cells, and does not shed. Germline transmission would require that the transgene be integrated into germline cells, which would require the presence of LVV. 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. If it were to occur, there are no deleterious effects of the transgene predicted.	Negligible
Genome integration in humans	KITE-585 comprises genetically modified, differentiated T cells, and does not shed viral particles. Therefore, there is no known mechanism for genome integration of the transgene to other cells in the patient. If free LVV particles were somehow to be present as an impurity in a KITE-585 preparation, because the vector is self-inactivating and replication deficient, it could integrate in the genome in a small number of cells, but vector would not be shed or spread further. If the LVV were to infect a small number of host cells, it would not confer selective advantage to the cells, or be predicted to cause deleterious effects.	Negligible
Disease or any other AE to animals or plants	KITE-585 comprises patients' own T cells containing an integrated CAR transgene delivered by an LVV. If exposed to animals, it is inconceivable how the human T cells, which do not survive outside of the human body, could enter and harm an animal. Since HIV-1 and LVV have a narrow tropism, confined to humans and chimpanzees, any AEs in plants are considered extremely unlikely.	Negligible
Population dynamics and genetic diversity of populations	KITE-585 cannot propagate in the environment, does not have microbial promoters and does not confer any selective advantage to any microorganism species. Therefore, no AE on population dynamics	Negligible

Adverse Effect	Potential Consequence	Magnitude (Severity)
	or genetic diversity of a population of microorganisms, and consequences, thereof, are to be expected.	
Facilitating the dissemination of infectious diseases	KITE-585 lacks pathogenic sequences that could be transferred to microorganisms, conferring selective advantage or pathogenic properties. AEs are not expected.	Negligible
Compromising prophylactic or therapeutic treatment	KITE-585 contains no sequences which would interfere with the prophylaxis or treatment of pathogenic microorganisms. Therefore, AEs are not expected.	Negligible
Disturbance of environmental biogeochemistry	The genetically modified T cells that comprise KITE-585 cannot survive outside of the body. Since the LVV is self-inactivating and replication-defective, the proliferation of the LVV is not possible. Therefore KITE-585 and the LVV are not expected to have any effect on biogeochemistry since they do not have the potential to proliferate and disseminate in the environment.	Negligible

Table 7. Likelihood of the Occurrence of Adverse Effects to People and the Environment

Adverse Effect	Occurrence	Likelihood
Adverse effects to humans	**Scenario: Self-inoculation** In the event that KITE-585 is administered to an unintended human recipient, such as through accidental injection to a medical practitioner, the engineered T cells would be rejected, and eliminated through the individual's innate (i.e. complement-mediated lysis and phagocytic cells) and adaptive immune system (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 if transmitted 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,	Very low

Adverse Effect	Occurrence	Likelihood
	cytopenias, infections, and tumor lysis syndrome. Additional details on AEs are provided in Table 6.	
	Scenario: Accidental Spillage The administration of KITE-585 will be performed at hospital centers by experienced health care professionals, appropriately trained in hygiene procedures and standards regarding safety and infectious materials handling. The adequate training of personnel for general infection prevention measures as well as the establishment and maintenance of training records on this item is the responsibility of the hospital centers as for all standard hospital procedures. All personnel on the site involved in handling or administration of KITE-585 will be demonstrably competent to handle KITE-585. KITE-585 contains autologous human T cells. Therefore, healthcare professionals should employ universal precautions for the prevention of transmission of blood-borne infections (Siegel et al, 2007). Established procedures for handling live human cells should be followed per the site guidelines and process. Once KITE-585 is administered to the patient, the intravenous (IV) bag along with the IV tubing and any other components that contain the product will be disposed of according to the site guidelines of GMO waste. All health care professionals involved in the administration will adhere to safe practices to avoid any release of the product into the environment. Work surfaces and material potentially in contact with KITE-585 will be decontaminated with 70% alcohol, according to hospital/facility hygiene procedures. In case of spillage, the spill is collected with a tissue soaked in 70% ethanol, and all contaminated waste including personal protective equipment (gloves, etc.) and bed sheets, in the appropriate hospital waste container.	Low

Adverse Effect	Occurrence	Likelihood
	Both T cells and any potential residual LVV particles in KITE-585 are susceptible to common methods of inactivation applied to microbial agents, and to many common virucidal disinfectants, including 1% sodium hypochlorite, 2% glutaraldehyde, formaldehyde and ethanol. In the event of accidental injection, enhanced bleeding out 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.	
	Scenario: theoretical exposure to any shed material • Exposure to third parties during medical procedures after infusion would not carry any risk if universal precautions are used (Siegel et al, 2007). • LVV is not shed from KITE-585 • No specific procedures are required within the clinical center. • The same applies in the case of unexpected death of the patient, requiring an autopsy. KITE-585 is not infectious. 293FT-K585 Vector sequences have integrated into the T-cell genome and there are no infectious 293FT-K585 Vector particles to be transmitted to healthcare personnel.	Negligible
Adverse effects to the environment	T cells such as those comprising KITE-585 cannot survive outside of the human body and would die rapidly if placed into a non-buffered *milieu*, such as waste water (Moore 1993). In case of an accidental spillage of a vial of KITE-585 during its administration to the patient, procedures as detailed in this table under "Scenario: accidental spillage" would inactivate KITE-585. Should LVV particles somehow be released into an aqueous environment, such as waste water, abundant with heterotrophic microorganisms and organic particles, LVV would be predicted to be inactivated rapidly, as free HIV-1 parent virus loses 99.9% of its infectivity by 8 h in water (Moore, 1993). Furthermore, KITE-585 presumably would be degraded or removed from waste water during waste treatment or, in case that waste water is not treated, by microbial activity in the effluent. Furthermore,	Negligible

Adverse Effect	Occurrence	Likelihood
	immobilization to solid particles can be expected. Therefore, it is highly unlikely that any adverse effect could happen in the environment.	

Abbreviations: AE, adverse event; BCMA, B cell maturation antigen; CRS, cytokine release syndrome; LVV, lentiviral vector; RCL, replication-competent lentivirus.

Table 8. Estimation of the Risk Posed by Each Identified Characteristic of the GMO

Adverse Effect	Exposure Type[a]	Magnitude / Severity	Likelihood	Overall Risk
Toxic effects to humans	Self-inoculation	Negligible [b]	Very low	Negligible
	Incidental exposure	Negligible [b]	Low	Negligible
Pathogenicity to humans	Self-inoculation	Negligible	Negligible	Negligible
	Incidental exposure	Negligible	Negligible	Negligible
Tumorigenicity to humans	Self-inoculation	Negligible	Negligible	Negligible
	Incidental exposure	Negligible	Negligible	Negligible
Germ-line transmission	Self-inoculation	Low	Negligible	Negligible
	Incidental exposure	Negligible	Negligible	Negligible
Genome integration in humans	Self-inoculation	Negligible	Negligible	Negligible
	Incidental exposure	Negligible	Negligible	Negligible
Disease or any other adverse effect to animals or plants	Incidental exposure	Negligible	Negligible	Negligible
Population dynamics and genetic diversity of populations	Incidental exposure	Negligible	Negligible	Negligible
Facilitating the dissemination of infectious diseases	Incidental exposure	Negligible	Negligible	Negligible
Compromising prophylactic or therapeutic treatment	Incidental exposure	Negligible	Negligible	Negligible
Disturbance of environmental biogeochemistry	Incidental exposure	Negligible	Negligible	Negligible

[a] Accidental self-inoculation by a healthcare professional, exposure = due to incidental spillage or shedding.

[b] Negligible for persons other than the patient.

4. ACTIVITY CLASS

The evidence presented herein demonstrates:

- Lack of a theoretical foundation for LVVs to cause human disease, and a clean clinical safety record: RCL have not been observed to form following infusion of LVV-transduced cells in clinical use (Holzinger et al, 2016; Naldini et al, 2016; Cornetta et al, 2018)
- Lack of a theoretical foundation for disease caused by genetically modified human T cells comprising KITE-585 to cause human disease, supported by the absence of such evidence in preliminary results with KITE-585. Early results from a first-in-human clinical study of KITE-585 have demonstrated an acceptable safety profile for the initial dose cohort, and early clinical efficacy results are promising (NCT 03318861). 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 (Berdeja et al, 2017; Brudno et al, 2017; Cohen et al, 2017; Smith et al, 2017).
- Inability of KITE-585 to survive in the environment based on the nature of T cells as reported in the literature
- Negligible likelihood of horizontal or vertical transmission of genetic material included in KITE-585

Based on these factors, KITE-585 is unlikely to have a deleterious effect on human health or to the environment. However, because KITE-585 comprises living human cells, it is Activity Class 2 (SACGM Compendium of guidance, part 2, page 35.)

5. CONCLUSIONS

The overall environmental risk of KITE-585 is concluded to be negligible, given the following considerations:

- The GMO (KITE-585) is not shed and cannot become persistent and invasive in natural habitats. The use of KITE-585 is limited to medical clinics where working instructions are based on the institutional guidelines for gene therapy to prevent spread to unintended persons
- There is negligible risk of recombination and RCL formation
- In case of vector contamination of KITE-585, there is no known or predicted potential for gene transfer from LVV to other species or even to humans other than the intended recipient, in the event of an accidental release to the environment
- There is no selective advantage or disadvantage conferred to the genetically modified T cells by lentiviral transduction. Following infusion, it is anticipated that the transduced T cells would not possess any selective growth advantage in vivo

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