EU Risk Management Plan for Tecartus

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RMP version to be assessed as part of this application:

Version number:	Data lock point for this RMP:	Date of final sign off:
5.0	**Clinical**: ZUMA-2: 24 July 2021 ZUMA-3: 23 July 2023 **Post-marketing**: 23 January 2024	Refer to Electronic Signature

Abbreviations: RMP = risk management plan

Rationale for submitting an updated RMP: Updated in response to the assessment report of the Tecartus 4th annual renewal.

Summary of significant changes in this RMP:

Part	Module/Annex	Significant Changes to RMP
Part I Product Overview		Not applicable
Part II Safety Specification	Part II: Module SI - Epidemiology of the Indication(s) and Target Populations(s)	Not applicable
	Part II: Module SII - Nonclinical Part of the Safety Specification	Not applicable
	Part II: Module SIII - Clinical Trial Exposure	Not applicable
	Part II: Module SIV - Populations Not Studied in Clinical Trials	Not applicable
	Part II: Module SV - Post-authorization Experience	Not applicable
	Part II: Module SVI - Additional EU Requirements for the Safety Specification	Not applicable
	Part II: Module SVII - Identified and Potential Risks	The safety specification includes the important potential risks of 'Secondary malignancy' and 'RCR'.
	Part II: Module SVIII - Summary of the Safety Concerns	The safety specification includes the important potential risks of 'Secondary malignancy' and 'RCR'.

Part	Module/Annex	Significant Changes to RMP
Part III Pharmacovigilance Plan		Removal of ZUMA-8 was considered again to reflect CSR submission.
Part IV Plan for Post-authorization Efficacy Studies		Not applicable
Part V Risk Minimization Measures		Updated to align with the Safety Specification updates.
Part VI Summary of the Risk Management Plan		Aligned with the changes made in the RMP.
Part VII Annexes	Annex 2, Annex 3	Updated to reflect changes made within the RMP.

Abbreviations: ALL = acute lymphoblastic leukemia; EU = European Union; MCL = mantle cell lymphoma; RCR = replication-competent retrovirus; RMP = risk management plan; SmPC = Summary of Product Characteristics.

Other RMP versions under evaluation

RMP Version number	Submitted on	Procedure number
None	Not applicable	Not applicable

Abbreviations: RMP = risk management plan

Details of the currently approved RMP:

Version number	Approved with procedure	Date of approval
4.0	EMEA/H/C/005102/WS2632/0041	25 April 2024

Abbreviations: RMP = risk management plan

QPPV name:	Anne-Ruth van Troostenburg de Bruyn
QPPV signature:	Refer to Electronic Signature

Abbreviations: QPPV = qualified person of pharmacovigilance

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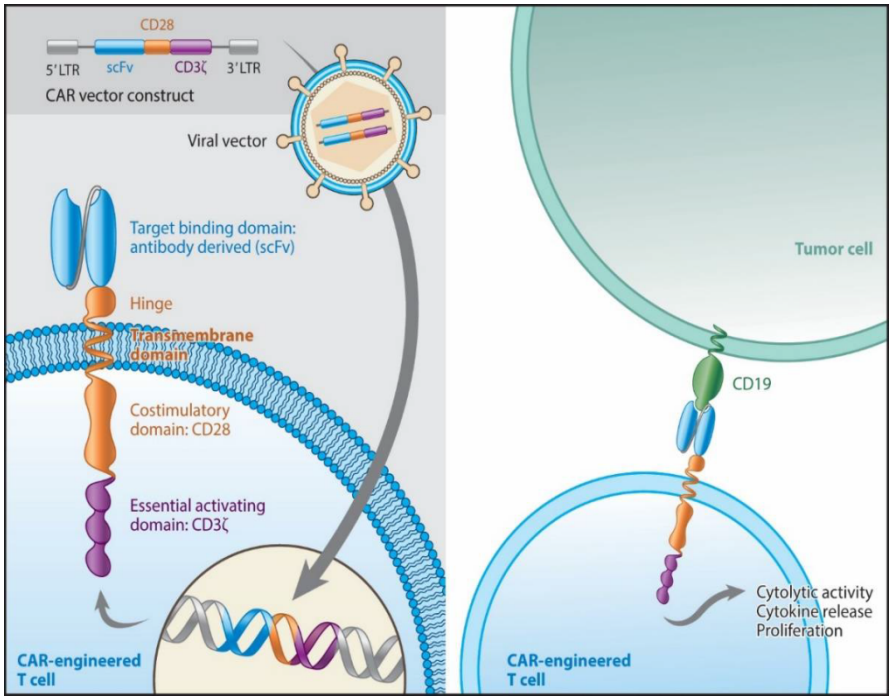
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ALL	acute lymphoblastic leukemia
Allo-SCT	allogeneic stem cell transplant
ATMP	advanced therapy medicinal product
B-ALL	B-cell precursor acute lymphoblastic leukemia
BTK	Burton's tyrosine kinase
CAR T	chimeric antigen receptor-engineered T-cells
CALGB	Cancer and Leukemia Group B
CD	cluster of differentiation
CNS	central nervous system
CR	complete remission
CRi	incomplete hematologic recovery
DoR	duration of remission
EU	European Union
HSC	hematopoietic stem cells
ICH	International Conference on Harmonisation
IR	incidence rate
mAb	monoclonal antibody
MCL	mantle cell lymphoma
MRD	minimal residual disease
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
OS	overall survival
PL	Package Leaflet
R-HyperCVAD	Rituximab-Hyperfractionated cyclophosphamide, vincristine, Adriamycin and dexamethasone
RCR	replication-competent retrovirus
RMP	risk management plan
scFv	single chain variable fragment
SmPC	summary of product characteristics
TKI	tyrosine kinase inhibitor
UK	United Kingdom
US	United States
VIS	vector integration sites
WBC	white blood count

PART I: PRODUCT OVERVIEW

Table Part I. 1. Product Overview

Active substance(s) (INN or common name)	Brexucabtagene autoleucel
Pharmaco-therapeutic group(s) (ATC Code)	L01XL06
Marketing Authorization Holder	Kite Pharma EU B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Tecartus
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class**: Not Applicable
	Summary of mode of action: Brexucabtagene autoleucel is an autologous cell-based product, by which a patient's own T cells are harvested and genetically engineered ex vivo by transduction using a γ-retroviral construct encoding an anti-CD19 CAR. As brexucabtagene autoleucel is an autologous cell-based product, it has no defined chemical properties. The anti-CD19 CAR construct used in the manufacturing process of brexucabtagene autoleucel comprises the following domains: an anti-human CD19 single-chain variable fragment; the partial extracellular domain and complete transmembrane and intracellular signaling domains of human CD28, a lymphocyte co-stimulatory receptor that plays an important role in optimizing T-cell survival and function; and the cytoplasmic portion, including the signaling domain, of human CD3ζ, a component of the T-cell receptor complex {Nicholson 1997}. Following CAR engagement with $CD19^+$ target cells, the CD3ζ domain activates the downstream signaling cascade that leads to T cell activation, proliferation, and acquisition of effector functions, such as cytotoxicity. The intracellular signaling domain of CD28 provides a co-stimulatory signal that works in concert with the primary CD3ζ signal to augment T-cell function, including IL-2 production {Finney 1998}. Together, these signals stimulate proliferation of the CAR T cells and direct killing of target cells. In addition, activated T cells secrete cytokines, chemokines, and other molecules that can recruit and activate additional antitumor immune cells {Restifo 2012}. A schematic describing the construct and the mode of action of the T-cell product is shown in the figure below.



Abbreviations: CAR = chimeric antigen receptor; CD = cluster of differentiation; LTR = long terminal repeat; scFv = single-chain variable fragment.

Important information about its composition: For production of brexucabtagene autoleucel, the anti-CD19 CAR construct is cloned into a retroviral vector and packaged into retroviral particles. T cells in the harvested leukocytes are enriched by binding to magnetic beads coated with anti-CD4 and anti-CD8 antibodies and then activated in culture with anti-CD3 and anti-CD28 antibodies before being transduced with a murine γ-retroviral vector that introduced the anti-CD19 CAR gene. Transduced cells are expanded in culture, washed, and cryopreserved to generate the product. Cryopreserved product is then shipped under controlled conditions to a treatment site, where the cells are thawed and infused into the patient.

Hyperlink to the Product Information	Tecartus (brexucabtagene autoleucel) Summary of Product Characteristics (SmPC)
Indication(s) in the EEA	**Current**: **Mantle Cell Lymphoma** Tecartus is indicated for the treatment of adult patients with relapsed or refractory MCL after two or more lines of systemic therapy including a BTK inhibitor. **Acute Lymphoblastic Leukemia** Tecartus is indicated for the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor ALL.
	Proposed: Not applicable

Dosage in the EEA	**Current**: MCL: Single infusion for autologous and intravenous use only. Each patient specific single infusion bag contains a dispersion of CAR-positive viable T cells in approximately 68 mL for a target dose of 2 x 10^6 CAR-positive viable T cells/kg body weight (range: 1 x 10^6 – 2 x 10^6 cells/kg), with a maximum of 2 x 10^8 CAR-positive viable T cells for patients 100 kg and above. ALL: Each patient specific single infusion bag contains a dispersion of CAR-positive viable T cells in approximately 68 mL for a target dose of 1 x 10^6 CAR-positive viable T cells/kg body weight, with a maximum of 1 x 10^8 CAR-positive viable T cells for patients 100 kg and above.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current**: Dispersion for infusion. Available as a clear to opaque, white to red dispersion. MCL: Each patient specific single infusion bag of Tecartus contains brexucabtagene autoleucel at a batch dependent concentration of autologous T cells genetically modified to express anti-CD19 CAR-positive viable T cells in approximately 68 mL. The medicinal product is packaged in one infusion bag overall containing a cell dispersion for infusion of a target dose of 2 x 10^6 anti-CD19 CAR-positive viable T cells/kg body weight (range: 1 x 10^6 – 2 x 10^6 cells/kg), with a maximum of 2 x 10^8 anti-CD19 CAR-positive viable T cells. ALL: Each patient specific single infusion bag of Tecartus contains brexucabtagene autoleucel at a batch dependent concentration of autologous T-cells genetically modified to express anti CD19 CAR-positive viable T cells in approximately 68 mL. The medicinal product is packaged in one infusion bag overall containing a cell dispersion for infusion of a target dose of 1 x 10^6 anti CD19 CAR-positive viable T cells/kg body weight, with a maximum of 1 x 10^8 anti CD19 CAR-positive viable T cells.
	Proposed: Not applicable
Is/Will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: ALL = acute lymphoblastic leukemia; ATC = anatomical therapeutic chemical; BTK = Bruton's tyrosine kinase; CAR = chimeric antigen receptor; CAR T = chimeric antigen receptor T cells; CD4 = cluster of differentiation 4; CD8 = cluster of differentiation 8; CD19 = cluster of differentiation 19; $CD19^+$ = cluster of differentiation 19-positive; CD28 = cluster of differentiation 28; CD3ζ = cluster of differentiation 3ζ; EEA = European Economic Area; EU = European Union; INN = international non-proprietary name; IL-2 = interleukin 2; MCL = Mantle cell lymphoma; RMP = risk management plan; SmPC = Summary of product characteristics.

PART II: SAFETY SPECIFICATION

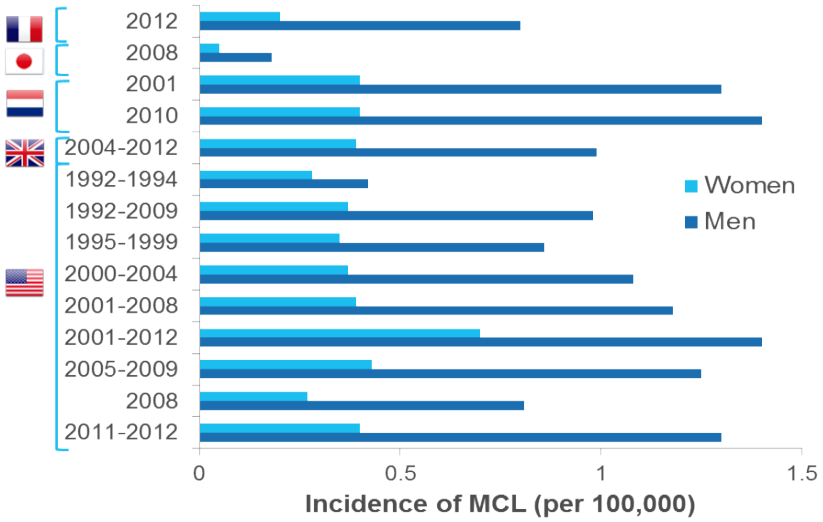
PART II: MODULE SI- EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1. Mantle Cell Lymphoma

SI.1.1. Incidence

Systematic literature review showed that the standardized Mantle cell lymphoma (MCL) incidence rates range from 0.1-1.27/100,000 (Figure SI. 1) {Monga 2020}.

Figure SI. 1. Standardized incidence rates of MCL by country and sex



Abbreviations: MCL = mantle cell lymphoma

SI.1.2. Prevalence

Based on incidence and survival data from the United Kingdom (UK)'s population-based Hematological Malignancy Research Network, the estimated 3-year prevalence of MCL is 1.8/100,000 (95% CI, 1.3-2.2) increasing to 2.4/100,000 (95% CI, 1.9-2.9) at 5 years, and to 3.3/100,000 (95% CI, 2.7-4.0) at 10 years. Prevalence among men is consistently higher than among women (2.3 vs 1.2/100,000, 3.4 vs 1.5/100,000, and 4.7 vs 2.0/100,000 at 3, 5, and 10 years, respectively) {Monga 2020}.

SI.1.3. Demographics of MCL

MCL patients are predominantly male (approximately 70%) and elderly (mean/median age ≥71 years). The higher incidence of MCL in men than in women, ranged from a ratio of 1.5:1 in the US during 1992–1994 to 4.0:1 in France in 2012, with most ratios being around 3:1 (Figure SI. 1) {Monga 2020}.

SI.1.4. Main Existing Treatment Options

Despite high response rates and improvement in survival with current frontline approaches, MCL patients inevitably relapse. Treatment options for relapse or refractory MCL is dependent on patient factors, prior therapy, remission duration, as well as candidacy for transplant. Preferred approved therapy options at relapse include chemotherapy, and the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib, while the approved agents bortezomib, lenalidomide, and temsirolimus have lower responses. Treatment options for relapsed or refractory MCL are summarized in Table SI. 1.

Table SI. 1. MCL treatment options

Class	Medicinal Product Brand name (generic name)	Safety Profile	Reference
mTOR Kinase inhibitor	Torisel (Temsirolimus)	The most serious reactions observed with temsirolimus are hypersensitivity/infusion reactions (including some life-threatening and rare fatal reactions), hyperglycemia/glucose intolerance, infections, interstitial lung disease (pneumonitis), hyperlipemia, intracranial hemorrhage, intestinal perforation, thrombocytopenia, neutropenia (including febrile neutropenia). The adverse reactions (all grades) experienced by at least 20% of the patients in MCL registration studies include anemia, nausea, rash (including rash, pruritic rash, maculopapular rash, pustular rash), decreased appetite, edema asthenia, fatigue, thrombocytopenia, diarrhea, pyrexia, epistaxis, mucosal inflammation, stomatitis, vomiting, hyperglycemia, hypercholesterolemia, dysgeusia, pruritus, cough, infection, pneumonia, and dyspnea.	{Torisel 2007}
Bruton's tyrosine kinase inhibitor	Imbruvia (Ibrutinib)	The most commonly occurring adverse reactions (≥20%) were diarrhea, neutropenia, musculoskeletal pain, rash, hemorrhage (eg, bruising), thrombocytopenia, nausea, pyrexia, arthralgia, and upper respiratory tract infection. The most common grade 3/4 adverse reactions (≥5%) were neutropenia, lymphocytosis, thrombocytopenia, pneumonia, and hypertension.	{IMBRUVICA 2014}

Class	Medicinal Product Brand name (generic name)	Safety Profile	Reference
Angiogenesis inhibitor. TNF-α inhibitor. Immunomodulatory effects	Revlimid (Lenalidomide)	The serious adverse reactions observed more frequently are neutropenia (3.6%), pulmonary embolism (3.6%), and diarrhea (3.6%). The most frequently observed adverse reactions were neutropenia (50.9%), anemia (28.7%), diarrhea (22.8%), fatigue (21.0%), constipation (17.4%), pyrexia (16.8%), and rash (including dermatitis allergic) (16.2%).	{REVLIMID 2017}
Proteasome inhibitor	Velcade (Bortezomib Accord) in combination with rituximab, cyclophosphamide, doxorubicin and prednisone	The most commonly reported adverse reactions during treatment with bortezomib are nausea, diarrhea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anemia, neutropenia, peripheral neuropathy (including sensory), headache, paresthesia, decreased appetite, dyspnea, rash, herpes zoster, and myalgia. Incidence of ≥ 5% higher of hematological adverse reactions (neutropenia, thrombocytopenia, leukopenia, anemia, lymphopenia), peripheral sensory neuropathy, hypertension, pyrexia, pneumonia, stomatitis, and hair disorders. Additional adverse drug reactions with the use of the combination therapy hepatitis B infection (< 1%) and myocardial ischemia (1.3%).	{VELCADE 2004}

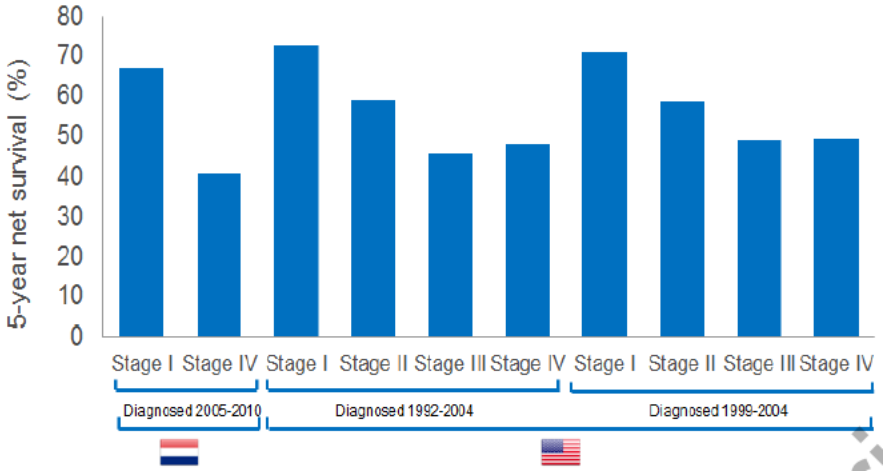
Abbreviation: MCL = mantle-cell lymphoma; mTOR = mammalian target of rapamycin; TNF-α = tumor necrosis factor-alpha

SI.1.5. Natural History of the Indicated Condition including Mortality and Morbidity

Patients typically present at an advanced stage disease at diagnosis, usually with generalized lymphadenomegaly, splenomegaly (30-50%), bone marrow infiltration (70-80%), peripheral blood involvement with circulating blasts, and frequent extranodal (extramedullary) involvement (40-50%), typically of the gastrointestinal tract {Klener 2017, Klener 2019}. Although MCL cases are often diagnosed at a moderately aggressive stage, the disease is clinically predicted to progress with age and show very poor long-term survival {Ghielmini 2004}.

Five-year net survival was poorer for patients with more advanced disease (5-year net survival: stage I, 67–72.6%; stage IV, 41–49.4%) (Figure SI. 2) {Monga 2020}.

Figure SI. 2. 5-year net survival in relapsed/refractory patients by disease stage (The Netherlands, United States)



SI.1.6. Important Co-morbidities

In terms of MCL, a population-based analysis was conducted using the Swedish Lymphoma Registry which identified the most prevalent comorbidities in MCL patients, between 2000 and 2015. Results showed that about 44% of patients had at least one comorbidity at diagnosis, of those just under 1 in 3 had two or more comorbidities {Glimelius 2018}. The most common comorbidities in MCL patients were as follows:

- Prior malignancy (17%; prostate cancer most frequent)
- Prior coronary heart disease (14%)
- Diabetes (9%)
- Pulmonary disease (7%)
- Renal disease (3%)
- Connective tissue disease (3%)
- Psychiatric disorder (2%)
- Dementia (1%)

SI.2. B-Cell Precursor Acute Lymphoblastic Leukemia

SI.2.1. Incidence

As B-ALL has been reported to represent approximately 85% of all ALL cases {Nahar 2009}, the age-standardized incidence of B-ALL in Europe is deduced to be 1.11 per 100,000 population in 2020 based on the CancerMpact registry ALL estimates {CancerMPact 2021}. A detailed listing of the crude and age-standardized incidence rates of ALL and B-ALL from data and literature sources is presented in Table SI. 2.

Table SI. 2. Crude and age-standardized incidence rates of ALL and B-ALL per 100,000 population at risk

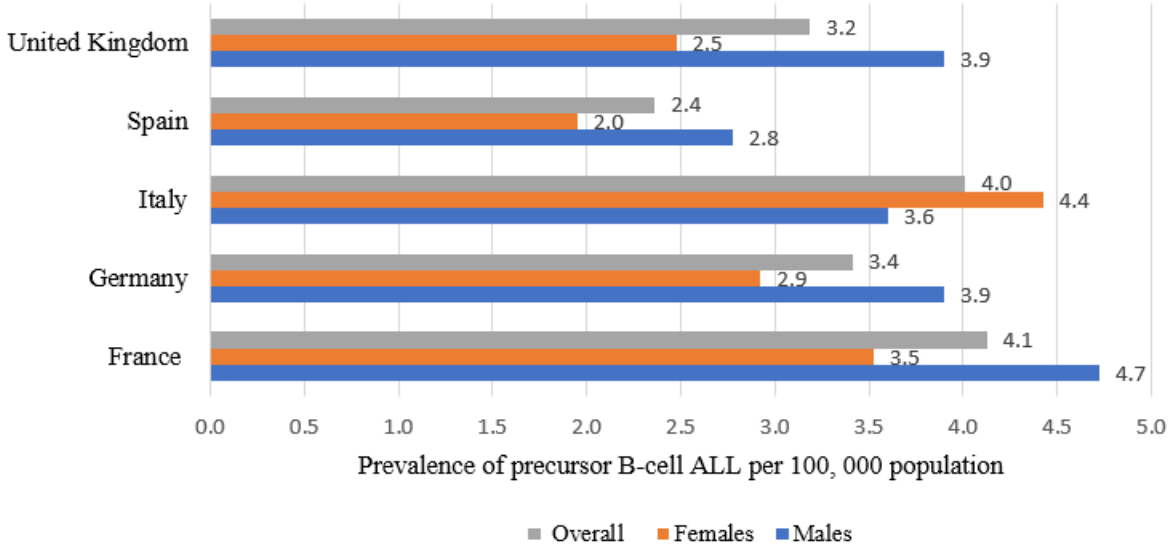
Source	Country	Period/Year	Crude Incidence Rate/100,000 population (95% CI)	Age-standardized Incidence Rate/ 100,000 population	Age-standardized Incidence Rate by sex/100,000 population	
					Male	Female
ALL						
{CancerMPact 2020}	Europe[a]	2020	-	1.30	1.40	1.20
{HMRN 2019}	United Kingdom	2010-2016	-	1.15	1.30	1.00
{Sant 2010}	44 European countries	2000-2002	1.28 (123-1.33)			
B-ALL						
{CancerMPact 2020}	Europe	2020	-	1.11[b]	1.19[b]	1.02[b]
{HMRN 2019}	United Kingdom	2010-2016	-	0.90	1.00	0.80
{Sant 2010}	44 European countries	2000-2002	0.08 (0.07-0.10)	-	-	-

Abbreviations: ALL = acute lymphoblastic leukemia; B-ALL = B-cell precursor acute lymphoblastic leukemia; CI = confidence interval; MCL = Mantle cell lymphoma.
a Countries: France, Germany, Italy, United Kingdom and Spain
b Incidence rates deduced from CancerMpact ALL estimates, by calculating 85% of ALL estimates

SI.2.2. Prevalence

The average 5-year prevalence rate of ALL reported in the CancerMpact registry was 4.6 per 100,000 population in 2020, ranging from 3.2 (Spain) to 5.5 (France) per 100,000 population. Given that 85% of all ALL cases in adults represent B-cell ALL {Nahar 2009}, an approximate 5-year prevalence of B-cell ALL is deduced to be 3.4 per 100,000 population (Figure SI. 3) {CancerMPact 2021}.

Figure SI. 3. Calculated prevalence rates (5-year) of B-ALL per 100,000 population for 5 European countries using CancerMPact data estimates overall and by sex, 2020



Source: CancerMpact

SI.2.3. Demographics of the population in B-ALL Indication

B-ALL risk is highest in children ≤ 5 years and lowest in adults in their mid-20s then peaks again slowly in adults aged 50 years and above {Loghavi 2015}. Males have been reported to have a slightly higher incidence rate of ALL in comparison to females: an average age-standardized male to female incidence ratio of 1.2:1 (1.4 versus 1.2) has been reported in the top 5 EU countries {CancerMPact 2021}. A similar trend is seen in the male to female ratio of age-standardized incidence rates for B-ALL which was reported as 1.3:1 (1.0 versus 0.8) in the HMRN registry {HMRN 2019}.

SI.2.4. Main Existing Treatment Options

First-line Treatment

Standard first-line treatment involves the use of several antineoplastic agents given in varying doses and schedules based on regional preferences and patient tolerability. Central nervous system (CNS) prophylaxis accompanies all phases of treatment {Jabbour 2005, National Comprehensive Cancer Network (NCCN) 2021}. The goals of treatment are to restore normal hematopoiesis, prevent emergence of treatment-resistant disease, eliminate minimal residual disease (MRD), and provide prophylaxis to sanctuary sites.

Most first-line regimens for ALL, regardless of immunophenotype, are a variation of either the Berlin-Frankfurt-Münster/Children's Oncology Group regimens, which include a combination of vincristine, an anthracycline, a corticosteroid, and L-asparaginase, or the Cancer and Leukemia Group B (CALGB) regimens, which include the 4 drug classes above plus cyclophosphamide {Larson 1995, Rowe 2005}. A tyrosine kinase inhibitor (TKI), such as imatinib or dasatinib, is included in the treatment regimen for patients with Philadelphia chromosome-positive (Ph+)

disease. One variation on the CALGB regimen includes alternating regimens of hyper-CVAD and has demonstrated efficacy in ALL {Kantarjian 2004}. First-line regimens yield complete remission (CR) rates of 80% to 90% in adults. However, despite the high CR rates and a median duration of first remission in most studies of ≥ 18 months, most patients eventually relapse {Kantarjian 2004, Larson 1995, Rowe 2005}.

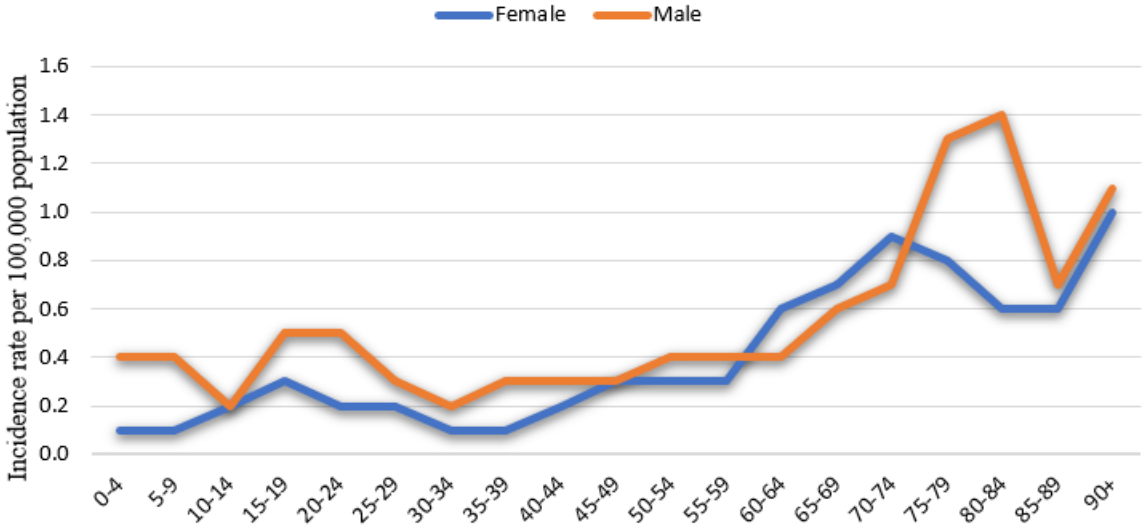
Allogeneic stem cell transplant (allo-SCT) remains the standard consolidation treatment in patients at high risk, who are fit and have an available donor.

SI.2.5. Natural History of the Indicated Condition including Mortality and Morbidity

For ALL, age and WBC have been reported to be predictors of poor prognosis and have been used in risk stratification. Age is a surrogate prognostic factor for characteristics that determine poor health outcomes such as presence of comorbidities, genetic mutations and intolerance to therapy {Terwilliger 2017}. Patients with higher WBC (>30 x 10 9/L for patients with B-ALL) at diagnosis were also reported to have poorer outcomes in comparison to patients with lower WBC. {Rowe 2005}.

An overall 5-year relative survival of ALL has been reported to be 66.5 % in the UK, with a higher survival rate being reported in young (<15 years) ALL patients than ALL patients aged ≥40 years during the period 2010-2016 {Haematological Malignancy Research Network (HMRN) 2021}. Males with ALL have been reported to have a slightly higher survival rate than females with ALL {Haematological Malignancy Research Network (HMRN) 2021}. During 2016-2018, age-specific mortality rates for ALL patients in the UK were reported to be 0.5 for males and 0.3 for females per 100,000 population {Cancer Research UK 2021}. The age-specific mortality rates for ALL remained stable in patients from birth until 50 years. A steep increase in mortality rate was observed in patients >50 years, and the highest mortality rates were reported in ALL patients aged >90 years (Figure SI. 4) {Cancer Research UK 2021}.

Figure SI. 4. Trends in age-specific mortality rates of ALL per 100,000 population at risk in the Cancer Research UK register, 2016-2018



Source: Cancer Research UK

SI.2.6. Important Co-morbidities

In terms of ALL, a multicenter study was conducted in Germany to provide data for pre-existing comorbidities associated with ALL in adults {Wermann 2018}. No publication was found to specifically report on co-morbidities for B-ALL. The most common comorbidities for adult patients with ALL were as follows:

- Infections (17%)
- Prior malignancies (16%)
- Diabetes (16%)
- Cardiac (14%) and moderate pulmonary disease (12%)
- Obesity (11%)
- Mild liver disease (10%).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Currently, no in vivo animal models are available for accurately assessing the nonclinical characteristics of a human autologous T-cell-based product such as brexucabtagene autoleucel. A relevant animal model would need to fulfill all the following criteria: 1) accurate expression of human CD19 in B cells, 2) presence of a fully competent and intact human immune system and repertoire, and 3) ability to support engraftment of human anti-CD19 chimeric antigen receptor T cells (CAR T) that would allow testing of the product candidate brexucabtagene autoleucel.

Further, according to both US and EU regulatory guidance documents {European Medicines Agency 2008, U.S. Department of Health & Human Services 2013}, the traditional battery of nonclinical studies establishing pharmacology, pharmacokinetics, and toxicity employed to support the development of drug products, such as a targeted small molecule or a biomolecule, are not applicable to an autologous cellular therapy such as brexucabtagene autoleucel .

Additionally, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines stipulate that therapeutics such as brexucabtagene autoleucel that are intended to treat patients with advanced cancers are exempted from the requirement for carcinogenicity studies {U.S. Department of Health and Human Services Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER) 2010}.

Based on the nature of brexucabtagene autoleucel and the guidance documents cited above, assessment of safety pharmacology endpoints, overall toxicology, reproductive and developmental toxicity, carcinogenicity, and genotoxicity using in vitro and in vivo models were not conducted.

The primary nonclinical data supporting the development of brexucabtagene autoleucel are leveraged from the data submitted in support of axicabtagene ciloleucel, Kite's first anti-CD19 CAR T-cell product, which is approved in multiple countries, including the US and EU. In addition, the nonclinical development package for brexucabtagene autoleucel also describes several in vitro characterization studies of brexucabtagene autoleucel that confirmed the in vitro functionality of brexucabtagene autoleucel. Importantly, brexucabtagene autoleucel and axicabtagene ciloleucel use the same anti-CD19 CAR construct, retroviral vector, and producer clone and follow a similar manufacturing process, except that the manufacture of brexucabtagene autoleucel includes a T-cell enrichment step and T-cell activation occurs in the presence of an anti-CD28 monoclonal antibody (mAb) in addition to an anti-CD3 mAb.

In addition to the brexucabtagene autoleucel in vitro functional characterization studies, the leveraged supportive nonclinical data include: 1) key published data demonstrating that CD19 expression is restricted to normal and malignant B-lineage cells and is not expressed on early hematopoietic stem cells (HSCs); 2) published in vitro studies characterizing the specificity and reactivity of human T cells transduced with anti-human CD19 CAR constructs (including the same anti-CD19 construct used in brexucabtagene autoleucel) towards $CD19^{+}$ target cells

{Kochenderfer 2009}; and 3) results for a surrogate anti-murine CD19 CAR construct tested both in vitro and in vivo in a syngeneic mouse model of a $CD19^+$ murine B-cell lymphoma {Kochenderfer 2010}. The surrogate anti-murine CD19 CAR construct was analogous to the anti-human CD19 construct used for brexucabtagene autoleucel. The anti-murine CAR construct comprised a single chain variable fragment (scFv) against murine CD19, the transmembrane and intracellular portions of murine CD28, and the intracellular domain of murine CD3-ζ. Thus, these surrogate studies in mice provide a nonclinical rationale for the expected antilymphoma effect of anti-CD19 CAR T cells in humans.

Product characteristics of engineered T cells from 15 subjects with advanced non-Hodgkin lymphoma (NHL) who received National Cancer Institute (NCI) anti-CD19 CAR T cells in the NCI Study 09-C0082 are presented as part of the nonclinical data supporting the development of Kite's anti-CD19 CAR T-cell products and are summarized herein. These studies were conducted to describe the effects of CAR T-cell activation on the production of cytokines, chemokines, and effector molecules that may contribute to the anticancer effect of anti-CD19 CAR T cells. These data are included here to support the specificity, selectivity, and polyfunctionality of the anti-CD19 CAR, which is the same construct as used in the manufacture of brexucabtagene autoleucel, as well as proof of concept that antitumor efficacy has been observed in clinical studies in addition to nonclinical studies, but is not meant to demonstrate or imply equivalence of the NCI product to the anti-CD19 CAR product manufactured with the brexucabtagene autoleucel process.

The initial in vitro characterization and nonclinical proof-of-concept studies were conducted by investigators at the NCI with their own anti-CD19 CAR T-cell product. Subsequent characterization studies were conducted collaboratively by Kite and the NCI or independently by Kite. Although the studies were not performed on a Kite anti-CD19 CAR T-cell product, the anti-CD19 CAR construct (FMC63-28Z), retroviral vector, and producer clone used in these studies and in the NCI Study 09-C-0082 were the same as used in the production of both brexucabtagene autoleucel and axicabtagene ciloleucel. Despite slight differences in the manufacturing process, direct comparison studies demonstrated comparability of the NCI product used to treat 15 subjects in NCI Study 09-C-0082 and axicabtagene ciloleucel, as shown by statistically equivalent transduction efficiency and similarity of in-process parameters, potency, and cell growth profiles. The manufacturing processes used to generate the NCI product and axicabtagene ciloleucel are also similar to the process used to manufacture brexucabtagene autoleucel, with the main differences being that brexucabtagene autoleucel is generated from $CD4^+$ and $CD8^+$ T cells that have been positively selected from the patient's apheresis material, and T-cell activation occurs in the presence of an anti-CD28 mAb in addition to an anti-CD3 mAb. Results of in vitro nonclinical characterization studies (T-cell activation, expansion, transduction, cytotoxicity, proliferation, and cytokine induction) confirm the in vitro functionality and CD19-specific cytotoxicity of the brexucabtagene autoleucel product and supplement the nonclinical data in support of brexucabtagene autoleucel.

Traditional genotoxicity studies are not applicable to cell-based products such as brexucabtagene autoleucel. Brexucabtagene autoleucel manufacturing relies on a murine γ-retroviral vector to stably integrate the anti-CD19 CAR transgene into the T-cell genome. The rationale for this vector selection is based on the following observations:

- Such retroviral vectors have been utilized for more than a decade by the NCI and other organizations to design diverse CAR and engineered T-cell receptor T-cell products for clinical evaluation.

- Findings to date, representing more than 23 months of follow-up for responders, have demonstrated successful human T-cell transduction and evidence of clinical efficacy in Phase 1 trials of an anti-CD19 CAR T-cell product produced at the NCI, utilizing the identical CAR and retroviral vector as used in brexucabtagene autoleucel and axicabtagene ciloleucel. Clinical results from the NCI study (Study 09-C-0082; NCT00924326) demonstrated 73% remission rate with 55% complete remissions and 18% partial remissions. Among patients with DLBCL, the overall remission rate was 68% with 47% CRs and 21% PRs, based on the investigator's assessment of response {Kochenderfer 2017a}. Clinical efficacy of axicabtagene ciloleucel is evidenced by complete remissions in 58% of treated patients (investigator's assessment; n = 101) and ongoing responses in 39% of patients at a median follow-up time of 27.1 months {Locke 2019}.

Although there is a theoretical risk of oncogenesis via insertional mutagenesis (ie, dysregulated activation of oncogenic genes at the site of vector integration in the host chromosome), no genotoxic/oncogenic effects manifested by transformation and clonal expansion resulting in T-cell malignancies have been observed in either animals or human subjects treated with γ-retrovirally transduced mature polyclonal T cells. The long-term safety profile of T-cell products that have been transduced with replication-defective γ-retroviral vectors is supported by additional data representing a period of up to approximately 5 years of follow-up for patients with solid tumors {Brentjens 2013, Robbins 2015} and 11 years (540-patient-years) for patients with HIV infection {Scholler 2012}. These studies have shown no evidence of long-term genotoxicity of T-cell therapies produced using γ-retroviral vectors. In addition, no evidence of long-term genotoxicity has been observed in subjects treated with anti-CD19 CAR T cells {Kochenderfer 2017a, Kochenderfer 2017b, Locke 2019}, which uses the same retroviral vector as used in the manufacture of brexucabtagene autoleucel.

The lack of genotoxicity observed in studies using γ-retroviral transduction of polyclonal T cells indicates that the safety issues observed with HSC do not translate to differentiated T cells and are not a general feature of retroviral vectors {Kochenderfer 2017a, Scholler 2012}. Taken together, the collective data from the published literature demonstrate that brexucabtagene autoleucel presents little risk for genotoxic effects. Additionally, a comprehensive summary of replication-competent retroviral (RCR) data derived from patients treated with ex vivo γ-retrovirally transduced T-cell products was performed on 629 follow-up samples ranging from 1 month to 8 years after infusion {Bear 2012}. The data demonstrated a lack of RCR events in patient samples across 29 clinical trials including HIV-infected patients. In addition, in Study KTE-C19-C101 (ZUMA-1), 2 year follow-up of subjects treated with axicabtagene ciloleucel, which is manufactured using the same retroviral vector as used for brexucabtagene autoleucel, no cases of RCR or axicabtagene-ciloleucel-related secondary cancers were observed {Locke 2019}. These findings support the safety of γ-retroviral vectors for engineering human T cells for therapeutic use.

Vector integration sites (VIS) were assessed in CAR T cells manufactured from healthy donor T cells transduced with a replication-incompetent murine γ-retroviral vector engineered to express the anti-CD19 CAR construct used in the manufacture of axicabtagene ciloleucel, and also used in the manufacture of brexucabtagene autoleucel. Results showed: 1) VIS were found preferentially near transcriptional start sites, which is consistent with VIS mapping for other murine γ-retroviral vectors reported in literature {Biasco 2011, Chang 2016}; and 2) strong distance association between VIS and T-cell-related genes, as expected of transcriptionally active chromatin at the time of vector integration, consistent with previous reports in the literature. The VIS characterization studies indicate that T-cell transformation due to murine γ-retroviral insertional mutagenesis would be an extremely rare event that likely requires the contribution of multiple additional factors beyond the integration site of the viral vector. Nevertheless, a risk monitoring approach is being used in clinical trials and the post-approval setting to characterize adverse events, such as secondary malignancies and presence of RCR, that have the potential to be related to genotoxicity {Chang 2019}.

Although studies to investigate the systematic γ-retroviral site integration analysis of the anti-CD19 CAR construct in the brexucabtagene autoleucel T-cell product could provide information on the proximity of the γ-retrovirus to certain genes or genomic regions, there is no evidence that this could be used as a prediction factor for a possible oligoclonal expansion. Additionally, as a technical limitation, the particular T-cell clone may not be detected in the infusion product due to a limitation of the sampling material or because of a combination of the relative abundance of the clone of interest and the resolution obtained with the available technologies. Interestingly, only 2 cases of clonal expansion due to viral integration in specific genomic regions of T cells have been reported to date in patients treated with CAR T-cell therapies in 2 independent clinical studies. In both cases, lentiviral vectors were used and both cases were characterized by a delayed clonal expansion of CAR T cells that contracted as the tumor was eliminated, without evidence of malignant transformation {Fraietta 2018, Shah 2019}. Notably, both CAR T-cell products were polyclonal at the end of manufacturing and the T cell clones responsible for the delayed expansion post-treatment were not detected in the infusion bags of either patient.

Thus, after careful review of the published literature regarding use of T-cell products produced using γ-retroviral vectors in addition to data collected for axicabtagene ciloleucel, Kite has concluded that additional studies of γ-retroviral site integration analysis in brexucabtagene autoleucel would not provide meaningful data.

PART II: MODULE SIII- CLINICAL TRIAL EXPOSURE

SIII.1. Clinical Trial Exposure

Cumulatively, until 23 January 2024, approximately 393 participants have been administered brexucabtagene autoleucel in the clinical trial program.

Table SIII 1. Cumulative Participant Exposure to brexucabtagene autoleucel from Ongoing Clinical Trials by Age and Sex (as of 23 January 2024)

Age (Years)	Male (N=183)	Female (N=89)	Total (N=272)
< 18	44	27	71
18 to 65	162	62	224
> 65	68	30	98
Total	274	119	393

Data cutoff date = 23JAN2024.
N = Participants treated with KTE-X19.
Compassionate use participants are not included.
Study KT-US-472-0141 is not included.
Data Source: ADSL Program Name: t_ex_age_sex Output Generated: 20240213T13:20

Table SIII 2. Cumulative Participant Exposure to brexucabtagene autoleucel from Ongoing Clinical Trials by Racial Group (as of 23 July 2021)

Racial group	Number of participants (N=272)
White	322
Other	40
Asian	10
Black or African American	8
Missing	10
Native Hawaiian or Other Pacific Islander	2
American Indian or Alaska native	1
Total	393

Data cutoff date = 23JAN2024.
N = Participants treated with KTE-X19.
Compassionate use participants are not included.
Study KT-US-472-0141 is not included.
Data Source: ADSL Program Name: t_ex_race Output Generated: 20240213T13:20

Table SIII. 3. Demographics in ZUMA-2

	Cohort 1 N(%) (N=68)	Overall N (%) (N=82)
Age (years)		
n	68	82
Mean (SD)	63.2 (7.9)	62.9 (7.5)
Median	65.0	65.0
Min, max	38, 79	38, 79
Age Category, n (%)		
<65 Years	29 (43)	40 (49)
≥65 Years	39 (57)	42 (51)
Sex, n (%)		
Male	57 (84)	68 (83)
Female	11 (16)	14 (17)
Ethnicity, n (%)		
Hispanic or Latino	11 (16)	13 (16)
Not Hispanic or Latino	55 (81)	67 (82)
Missing	2 (3)	2 (2)
Race, n (%)		
Black or African American	1 (1)	1 (1)
White	62 (91)	75 (91)
Native Hawaiian or other Pacific Islander	1 (1)	1 (1)
Others	4 (6)	5 (6)
Country, n (%)		
United States	62 (91)	76 (93)
France	3 (4)	3 (4)
Netherlands	2 (3)	2 (2)
Germany	1(1)	1 (1)

Data cutoff date = 24 July 2021
Abbreviations: N = number of subjects treated.
Note: Percentages are based on the number of subjects treated
Source: ZUMA-2 24 months CSR

Table SIII. 4. Demographics in ZUMA-3 (Phase 1 and Phase 2, Safety Analysis Set; N=100)

	Phase 1 and Phase 2 (N = 100)
Age (years)	
n	100
Mean (Std Dev)	43.4 (16.3)
Median	44.0
Min, Max	18, 84
Age category, n (%)	
< 65 Years	85 (85)
≥ 65 Years	15 (15)
Sex, n (%)	
Male	55 (55)
Female	45 (45)
Ethnicity, n (%)	
Hispanic or Latino	28 (28)
Not Hispanic or Latino	70 (70)
Missing	2 (2)
Race, n (%)	
American Indian or Alaska Native	1 (1)
Asian	6 (6)
Black or African American	1 (1)
Native Hawaiian or Other Pacific Islander	1 (1)
White	76 (76)
Other	11 (11)
Missing	4 (4)
Country of enrolled sites, n (%)	
Germany	3 (3)
France	10 (10)
Netherlands	1 (1)
United States	86 (86)

Data cutoff date = 09Sep2020.
Abbreviations: Std Dev = standard deviation.
Note: Percentages are based on the number of subjects treated with any dose of KTE-X19.
Data Source: ADSL Program Name: t_dm Output Generated: 20210406T08:12
Source: Table 14.1.3.4

Table SIII. 5. Summary of Follow-up Time in ZUMA-2

	Cohort 1	Overall
Potential follow-up time from KTE-X19 infusion (month)[a]		
N	68	82
Mean (SD)	40.4 (9.7)	40.3 (8.9)
Median (Q1, Q3)	35.6 (32.4, 50.6)	38.0 (32.8, 50.1)
Min, max	25.9, 56.3	25.9, 56.3
Subjects with ≥ 1 month potential follow-up[b], n (%)	68 (100)	82 (100)
Subjects with ≥ 3 months potential follow-up[b], n (%)	68 (100)	82 (100)
Subjects with ≥ 6 months potential follow-up[b], n (%)	68 (100)	82 (100)
Subjects with ≥ 9 months potential follow-up[b], n (%)	68 (100)	82 (100)
Subjects with ≥ 12 months potential follow-up[b], n (%)	68 (100)	82 (100)
Subjects with ≥ 15 months potential follow-up[b], n (%)	68 (100)	82 (100)
Subjects with ≥ 18 months potential follow-up[b], n (%)	68 (100)	82 (100)
Subjects with ≥ 24 months potential follow-up[b], n (%)	68 (100)	82 (100)
Subjects with ≥ 30 months potential follow-up[b], n (%)	60 (88)	74 (90)
Subjects with ≥ 36 months potential follow-up[b], n (%)	32 (47)	46 (56)

Data cutoff date = 24 July 2021.
Abbreviations: N = number of subjects treated; Q1 = first quartile; Q3 = third quartile.
Note: Percentages are based on the number of subjects enrolled (leukapheresed).
a Potential follow-up time is calculated as the time from KTE-X19 infusion to the data cutoff date.
b Percentages are based on the number of subjects treated.
Source: Modified from Table 14.1.2.1a and Table 14.1.2.1c

Table SIII. 6. Summary of Follow-up Time in ZUMA-3 (Phase 1, Safety Analysis Set; N=54)

	Phase 1 (N = 54)
Actual follow-up time from KTE-X19 dose (months) [a]	
n	45
Mean (Std Dev)	25.6 (26.8)
Median (Q1, Q3)	11.4 (3.4, 57.2)
Min, Max	0.2, 83.9
Potential follow-up time from KTE-X19 dose (months) [b]	
n	45
Mean (Std Dev)	72.2 (8.5)
Median (Q1, Q3)	73.8 (65.1, 76.4)
Min, Max	58.8, 87.9
Subjects with ≥ 1 month potential follow-up [b], n (%)	45 (100)
Subjects with ≥ 3 months potential follow-up [b], n (%)	45 (100)
Subjects with ≥ 6 months potential follow-up [b], n (%)	45 (100)
Subjects with ≥ 9 months potential follow-up [b], n (%)	45 (100)
Subjects with ≥ 12 months potential follow-up [b], n (%)	45 (100)
Subjects with ≥ 15 months potential follow-up [b], n (%)	45 (100)
Subjects with ≥ 18 months potential follow-up [b], n (%)	45 (100)
Subjects with ≥ 24 months potential follow-up [b], n (%)	45 (100)
Subjects with ≥ 30 months potential follow-up [b], n (%)	45 (100)
Subjects with ≥ 36 months potential follow-up [b], n (%)	45 (100)
Subjects with ≥ 42 months potential follow-up [b], n (%)	45 (100)
Subjects with ≥ 48 months potential follow-up [b], n (%)	45 (100)
Subjects with ≥ 54 months potential follow-up [b], n (%)	45 (100)
Subjects with ≥ 60 months potential follow-up [b], n (%)	40 (89)
Subjects with ≥ 66 months potential follow-up [b], n (%)	31 (69)
Subjects with ≥ 72 months potential follow-up [b], n (%)	28 (62)
Subjects with ≥ 78 months potential follow-up [b], n (%)	11 (24)
Subjects with ≥ 84 months potential follow-up [b], n (%)	3 (7)

Data cutoff date = 23Jul2023
Abbreviations: CSF, cerebrospinal fluid; Q1, first quartile; Q3, third quartile; STDEV, standard deviation.
Note: Percentages are based on the number of subjects enrolled (leukapheresed).
2e6 = 2 × 106 anti-CD19 CAR T cells/kg; 1e6 = 1 × 106 anti-CD19 CAR T cells/kg; 0.5e6 = 0.5 × 106 anti-CD19 CAR T cells/kg.

a. Actual follow-up time from KTE-X19 dose is calculated as (death date or last date known alive – KTE-X19 infusion date + 1)/30.4375. For retreatment subjects, the initial KTE-X19 infusion date was used.
b. Potential follow-up time is calculated as (the cutoff date – the KTE-X19 infusion date + 1)/30.4375. For retreated subjects, the initial KTE-X19 infusion date was used. Percentages are based on the number of subjects treated.

Data Source: ADSL Program Name: t_ds1 Output Generated: 20230919T11:30

Table SIII. 7. Summary of Follow-up Time in ZUMA-3 (Phase 2, Safety Analysis Set; N=71)

	Phase 2 (N = 71)
Actual follow-up time from KTE-X19 dose (months) [a]	
n	55
Mean (Std Dev)	25.1 (18.4)
Median (Q1, Q3)	23.5 (7.6, 42.4)
Min, Max	0.3, 54.3
Potential follow-up time from KTE-X19 dose (months) [b]	
n	55
Mean (Std Dev)	51.1 (3.4)
Median (Q1, Q3)	50.8 (48.2, 54.0)
Min, Max	44.7, 56.5
Subjects with ≥ 1 month potential follow-up [b], n (%)	55 (100)
Subjects with ≥ 3 months potential follow-up [b], n (%)	55 (100)
Subjects with ≥ 6 months potential follow-up [b], n (%)	55 (100)
Subjects with ≥ 9 months potential follow-up [b], n (%)	55 (100)
Subjects with ≥ 12 months potential follow-up [b], n (%)	55 (100)
Subjects with ≥ 15 months potential follow-up [b], n (%)	55 (100)
Subjects with ≥ 18 months potential follow-up [b], n (%)	55 (100)
Subjects with ≥ 24 months potential follow-up [b], n (%)	55 (100)
Subjects with ≥ 30 months potential follow-up [b], n (%)	55 (100)
Subjects with ≥ 36 months potential follow-up [b], n (%)	55 (100)
Subjects with ≥ 42 months potential follow-up [b], n (%)	55 (100)
Subjects with ≥ 48 months potential follow-up [b], n (%)	42 (76)
Subjects with ≥ 54 months potential follow-up [b], n (%)	13 (24)

Data cutoff date = 23Jul2023
Abbreviations: CSF, cerebrospinal fluid; Q1, first quartile; Q3, third quartile; STDEV, standard deviation.
Note: Percentages are based on the number of subjects enrolled (leukapheresed).
a. Actual follow-up time from KTE-X19 dose is calculated as (death date or last date known alive – KTE-X19 infusion date + 1)/30.4375. For retreatment subjects, the initial KTE-X19 infusion date was used.
b. Potential follow-up time is calculated as (the cutoff date – the KTE-X19 infusion date + 1)/30.4375. For retreated subjects, the initial KTE-X19 infusion date was used. Percentages are based on the number of subjects treated.
Data Source: ADSL Program Name: t_ds2 Output Generated: 20230919T11:30

PART II: MODULE SIV- POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1. Exclusion Criteria in Pivotal Clinical Studies within the Development Program

Table SIV. 1. Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Considered to be Missing Information
Primary immunodeficiency. Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous antimicrobials for management. Live vaccine ≤ 6 weeks prior to planned start of conditioning regimen. Known history of human HIV infection or acute or chronic active hepatitis B or C infection. Subjects with a history of hepatitis infection must have cleared their infection as determined by standard serological and genetic testing (ZUMA-2 and ZUMA-3).	These patients were excluded from participation in the clinical trial as they were at greater risk of infection due to: brexucabtagene autoleucel being associated with B-cell aplasia (which leads to hypogammaglobulinaemia); lymphodepletion per study protocol (from conditioning chemotherapy) which may result in cytopenias and hypogammaglobulinaemia; infection associated with administration of live vaccine; possibility of a synergistic effect on the immune system since live vaccines also stimulate the immune system and this may have resulted in difficulties in the interpretation of safety and efficacy data.	No **Rationale**: Cytopenias, especially prolonged cytopenias and infections, especially serious infections, are Important Identified Risks and will be described in the SmPC.
History of severe, immediate hypersensitivity reaction attributed to aminoglycosides or to any agent used in studies (ZUMA-2 and ZUMA-3).	May have affected safety outcomes	No **Rationale**: History of hypersensitivity to the product or any of its excipients will be a contraindication for use and hence it is not relevant to include as Missing Information.
Women of childbearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant. Subjects of both genders who are not willing to practice birth control from the time of consent through 6 months after completion of brexucabtagene autoleucel (ZUMA-2 and ZUMA-3).	No animal data available. Due to the known reproductive toxicity with the chemotherapy used for conditioning the patients, women of childbearing potential or who were pregnant, or breast feeding were excluded for safety reasons.	No **Rationale**: Exposure in patient population unlikely due to high median age of patients, pre-treatment with conditioning chemotherapy, and male predominance in MCL diagnosis.

Criterion	Reason for Exclusion	Considered to be Missing Information
History of autoimmune disease (eg, Crohn's disease, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years (ZUMA-2 and ZUMA-3).	These patients were excluded as it was not known whether stimulation of the immune system by brexucabtagene autoleucel would result in reactivation of immune disorders. Expansion of T-cells and potentially self-reactive T-cells may also place these patients at a higher risk of reactivation of autoimmune disorders.	Yes **Rationale:** Not applicable
Subjects with detectable cerebrospinal fluid malignant cells or brain metastases or with a history of CNS lymphoma, cerebrospinal fluid malignant cells, or brain metastases. History or presence of CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, cerebral edema, posterior reversible encephalopathy syndrome, or any autoimmune disease with CNS involvement* (ZUMA-2 and ZUMA-3).	Anti-CD19 CAR T-cell therapies are associated with neurologic effects and inclusion of these patients would have confounded the safety endpoints of the study.	No **Rationale**: Serious neurologic adverse reactions including cerebral edema is an Important Identified Risk and will be described in the SmPC.
History of malignancy other than non-melanomatous skin cancer or carcinoma in situ (eg, cervix, bladder, breast) unless disease-free for at least 3 years (ZUMA-2 and ZUMA-3).	Inclusion of these patients would have affected the safety and efficacy endpoints of the study, eg, relapse or progression of the malignancy can cause misinterpretation of the endpoints.	No **Rationale**: Secondary malignancy is considered an Important Potential Risk and will be described in the SmPC.
History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease. History of symptomatic deep vein thrombosis or pulmonary embolism (ZUMA-2 and ZUMA-3).	To avoid confounding evaluation of safety.	No **Rationale**: Cardiotoxicity could be increased during the CRS manifestation. As CRS is considered an important identified risk, physicians will be aware of the risk. Thus, use in this population will not be considered missing information.
History of concomitant genetic syndrome associated with bone marrow failure such as Fanconi anemia, Kostmann syndrome, Shwachman-Diamond syndrome (ZUMA-3).	To avoid confounding evaluation of efficacy.	No **Rationale**: These syndromes are rare.

Criterion	Reason for Exclusion	Considered to be Missing Information
Presence of any indwelling line or drain/catheters.	To avoid confounding evaluation of safety.	No **Rationale**: The safety profile in these patients is not expected to differ from the known safety profile. 'Infections' is considered an important identified risk.

Abbreviations: CAR T = chimeric antigen receptor T cells; CD19 = cluster of differentiation 19; CNS = central nervous system; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; MCL = Mantle cell lymphoma; SmPC = summary of product characteristics.
* In ZUMA-3, subjects with CNS-1 (no detectable leukemia in the CSF) and those with CNS-2 without clinically evident neurological changes were eligible to participate in the study.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

Table SIV. 2. Ability of the Clinical Trial Development Program to Detect Adverse Drug Reactions

Ability to Detect Adverse Reactions	Limitation of Trial Program	Discussion of Implications for Target Population
Which are rare	As of the data cut-off date of 24 July 2021, 82 subjects have been exposed to brexucabtagene autoleucel in the ZUMA-2 clinical trial. In the ALL, ZUMA-3 clinical trial, as of the data cut-off of 23 July 2023, 100 subjects have been exposed to brexucabtagene autoleucel.	ADRs with a frequency greater than 1 in 61 could be detected if there were no background incidence.
Due to prolonged exposure	In the MCL, ZUMA-2 clinical trial as of 24 July 2021, the median actual follow-up time was 32.4 months (range: 0.6 to 56.3 months). In the ALL, ZUMA-3 clinical trial, 100 subjects have been exposed to brexucabtagene autoleucel. The median (Q1, Q3) follow-up time from exposure to brexucabtagene autoleucel to the data cut-off of 23 July 2023 was 25.6 (26.8) months for Phase 1 and 23.5 (7.6, 42.4) months for Phase 2.	Brexucabtagene autoleucel is given as a single dose, therefore no cumulative effects have been identified.
Due to cumulative effects	In the MCL, ZUMA-2 clinical trial, brexucabtagene autoleucel has been given as a single dose to 82 subjects, with 3 subjects undergoing retreatment. In the ALL, ZUMA-3 clinical trial, brexucabtagene autoleucel has been given as a single dose to 100 subjects, with 5 subjects undergoing retreatment.	There is no risk of cumulative effects.
Which have a long latency	For ZUMA-2, the post-exposure observation time in clinical trials is limited to up to 56 months as of 24 July 2021. For ZUMA-3, the post-exposure observation time in clinical trials is limited up to 84 months as of 23 July 2023.	There is no evidence of new signals in subjects who were followed for up to 84 months.

Abbreviations: ADR = adverse drug reaction; ALL = acute lymphoblastic leukemia; MCL = mantle cell lymphoma; Q1 = first quartile; Q3 = third quartile.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table SIV. 3. Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of special population	Exposure
Elderly population	In ZUMA-2, 51% of subjects were ≥ 65 years In ZUMA-3, 15% of subjects were ≥ 65 years respectively.
Pediatric population	Not included in the clinical development program
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities: • Patients with moderate to severe hepatic impairment • Patients with moderate to severe renal impairment • Patients with cardiovascular disease • Immuno-compromised patients	Not included in the clinical development program
Population with relevant different ethnic origin	In ZUMA-2: White 91%, Black or African American 1%, Native Hawaiian or other Pacific Islander 1%, Others 6% Hispanic or Latino 16%, Not Hispanic or Latino 82% ZUMA-3: White 76%, Asian 6%, Black of African American 1%, Native Hawaiian or Other Pacific Islander 1%, American Indian or Alaska Native 1%, Other 11%, Missing 4%, Hispanic or Latino 28%, Not Hispanic or Latino 70%
Subpopulations carrying known and relevant genetic polymorphisms	Not applicable

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1. Post-Authorization Exposure

SV.1.1. Method used to calculate exposure

Patient exposure to brexucabtagene autoleucel was estimated using distribution data. It should be noted that the use of distribution data for patient exposure calculations may overestimate patient exposure as not every patient will ultimately receive treatment.

SV.1.2. Exposure

Estimated cumulative patient exposure to brexucabtagene autoleucel in the commercial setting since first marketing approval (24 July 2020; US) to 23 January 2024 is estimated to be 2722. The estimated cumulative exposure to brexucabtagene autoleucel in the commercial setting can be found in Table SV.1 below.

Table SV.1 Exposure by Geographic Area

Geographic Area	Estimated Patient Exposure Cumulatively
USA	1676
EEA[a]	771
Great Britian [b]	164
Switzerland	26
Israel	35
Canada	41
Australia	9
Total[c]	**2722**

Abbreviations: EEA = European Economic Area; USA = United States of America.

a European Economic Area (EEA) - Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland (including Northern Ireland), Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden

b Great Britain – England, Scotland, Wales (not including Northern Ireland)

c A total of 248 brexucabtagene autoleucel lots have been shipped in the expanded access setting cumulatively in the US, Canada, Great Britain, Switzerland, Australia, and EEA countries and are not included in the total from the commercial setting.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1. Potential for Misuse for Illegal Purposes

There is no data to suggest that there is potential for brexucabtagene autoleucel to be misused for illegal purposes. Furthermore, its manufacture and supply are patient-specific and the supply chain would not provide any opportunity for misuse for illegal purposes. Thus, this is not a safety concern.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1. Identification of Safety Concerns in the Initial RMP submission

SVII.1.1. Risk(s) not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table SVII. 1. Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Recognizing that brexucabtagene autoleucel is classified as an advanced therapy medicinal product (ATMP), an overview of ATMP-specific considerations, including risks that are not considered important for inclusion in the list of safety concerns, is provided below.

Reason	List of Risks	Assessment
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	Harvesting T cells (leukapheresis)	Risks include decrease in white blood cells, hypocalcemia, blood loss, discomfort at venous site, local infection at venous site.
	Product quality characteristics and storage and distribution of the product	Retroviral vector lots are tested for sterility, adventitious agents including mycoplasma and infectious virus, RCR and viral potency prior to release for use in the brexucabtagene autoleucel manufacturing process. The product will be released after the completion of a validated sterility test therefore as long as the bag is not compromised, contents should be free of bacterial contaminants. The product needs to be kept cryopreserved and stored in a vapor phase liquid nitrogen freezer. When stored in this condition the product has been shown to be stable for at least 1 year. The product is shipped in a validated liquid nitrogen vapor phase shipper. Product will remain stable throughout shipping duration. The product remains stable for up to 3 hours post-thaw; however, it is recommended that dosing is completed 30 minutes post thaw. All doses are stored and shipped frozen. Thawing occurred immediately prior to infusion for all subjects treated to date. The freeze/thaw procedures have been shown to be safe. Autologous product, therefore, the subjects' own leukapheresis material is being used to manufacture brexucabtagene autoleucel, therefore the risk of a transmissible disease is low. Manufacturing is conducted using single use components, therefore transmission from one lot to another is unlikely.
	Administrative procedures	Brexucabtagene autoleucel is administered intravenously and no adverse events associated with intravenous administration, such as injection site reactions have been observed.
	Persistence of the product in the patient	The retroviral vector construct is an integral part of the transduced T cell genome; however, generally the transduced T cells do not persist for an extended period within the patient following treatment with brexucabtagene autoleucel. Evidence to date showed that the median days to peak of anti-CD19 CAR T cells levels in blood was 15 days after brexucabtagene autoleucel infusion and levels decreased to near background levels by Month 3. In the MCL, ZUMA-2 clinical trial, low levels of anti-CD19 CAR T cells were still detectable in 6 of 10 subjects with evaluable samples at Month 24. In the ALL, ZUMA-3 clinical trial, the anti-CD19 CAR T cells were still detectable in 2 of 20 subjects with evaluable samples at Month 12.

Reason	List of Risks	Assessment
	Risk to health care professionals, care givers, offspring and other close contacts with the product (retroviral vector) or its components	Anti-CD19 transduced T cells, like natural T cells, are easily inactivated outside the host by inappropriate media, or exposure to low pH, higher temperatures (>50°C), pasteurization (60°C for 10 hours), and microwave. Cells present in brexucabtagene autoleucel are easily killed by lipid solvents, alcohol and disinfectants. **Shedding** Retroviral particles that have not entered and transduced the T cells are removed during the manufacturing process and have a short half-life under the cultured conditions {Merten 2004}. Therefore, it is considered that there is a negligible number of cell-free retroviral vector particles infused into the patient. In general, autologous T cells transduced with retroviral particles are not considered true excreta since they do not shed into the environment spontaneously {Schenk-Braat 2007}. The patients' own ex vivo modified T cells are not shed via saliva, urine, or feces into the environment, including wastewater. Any released retroviral vector construct cannot be transmitted by air and is not expected to be infectious. **Patient Samples** The patient samples such as blood, bone marrow or lymph node biopsy samples cannot contain free viral vector but will contain the patients engineered T cells which are not pathogenic, do not replicate or survive outside the patient. Brexucabtagene autoleucel contains negligibly low levels of free viral vector. Any potential remaining viral vector particles in the product would be inhibited/inactivated by the complement component of human serum after administration to the patient {Chira 2015, Welsh 1975, Welsh 1976}. Theoretically, if anti-CD19 CAR T cell membrane integrity is challenged and any gammaretroviral vector that has not incorporated into the host chromatin is released into an aqueous environment, such as waste water, abundant with heterotrophic microorganisms and organic particles, it can be assumed that the gamma-retroviral vector PG13- CD19-H3 Vector, if present at all, will be either degraded by microorganisms or adsorbed onto particles quickly (World Health Organization (WHO) 1979). **Accidental injection** In the event that the retroviral vector construct is transmitted through accidental injection, the immune system of medical personnel (or other individuals), would eliminate the cells via their immune system and not experience adverse effects beyond a normal immune reaction. Thus, no lasting negative consequences are expected in the event that an accidental injection occurs.
Other reasons for considering the risks not important	Conditioning chemotherapy	Bone marrow suppression is a recognized effect of conditioning chemotherapy with cyclophosphamide and fludarabine. CNS risks with fludarabine are recognized events as well. Such effects are well-known to clinicians and risk minimization measures are part of standard clinical practice for these risks. The risks are therefore not classified as important as per the guidance on GVP Module V.

Abbreviations: ALL = acute lymphoblastic leukemia; CAR T = chimeric antigen receptor T cells; CD19 = cluster of differentiation 19; CNS = central nervous system; GVP = Good pharmacovigilance practices; MCL = mantle cell lymphoma; RCR = replication-competent retrovirus.

SVII.1.2. Risk(s) Considered Important for Inclusion in the List of Safety Concerns in the RMP

SVII.1.2.1. Important Identified Risks

Table SVII. 2. Important Identified Risks

Important Identified Risks	Risk-Benefit Impact
Serious neurologic events including cerebral edema	Serious neurologic events including cerebral edema have been identified as expected events during therapy with brexucabtagene autoleucel. Neurologic events observed in clinical trial subjects treated with brexucabtagene autoleucel have generally been manageable and reversible with supportive care measures, corticosteroids, and, in the setting of CRS, tocilizumab. Severe neurologic events that required ventilation and/or management in the intensive care setting have occurred in clinical trial subjects treated with brexucabtagene autoleucel. In ZUMA-2 68% of subjects had neurologic events. The most common neurologic events of any grade were tremor (38%), followed by encephalopathy (26%), confusional state (24%), aphasia (18%), somnolence (11%), agitation (9%), lethargy (9%), memory impairment (9%), and disturbance in attention (6%). The most common Grade 3 or higher neurologic events were encephalopathy (16%), confusional state (11%), and aphasia (5%). Overall, 33% of subjects had a Grade 3 or higher neurologic event (26% had worst Grade 3 events and 7% had worst Grade 4 events). No subject had a Grade 5 neurologic event. In ZUMA-3, 68% of subjects had neurologic events. The most common neurologic events of any grade were confusional state (29%), encephalopathy (29%), tremor (28%), aphasia (22%), agitation (13%), seizure (8%), delirium (6%) and somnolence (6%). The most common Grade 3 or higher neurologic events were encephalopathy (15%), aphasia (13%) and confusional state (6%). Overall, 32% of subjects had a grade 3 or higher neurologic event (27% had worst Grade 3 events and 4% had worst Grade 4 events, and 1 subject had a grade 5 event of brain herniation). HCPs should monitor patients for signs and symptoms of neurologic adverse reactions and manage the risks as advised in the risk minimization measures. Neurologic adverse events can be serious and potentially life-threatening, and proper monitoring and treatment are required to minimize the risk and to ensure an acceptable risk-benefit balance.
CRS	CRS has been identified as an expected event during therapy with brexucabtagene autoleucel. Organ-specific toxicities may also be observed as part of CRS {Lee 2014}. CRS observed in clinical trial subjects treated with brexucabtagene autoleucel has generally been manageable and reversible with supportive care measures, tocilizumab, and/or corticosteroids. Severe cases of CRS that required vasopressor support or mechanical ventilation have occurred in clinical study subjects treated with brexucabtagene autoleucel. In ZUMA-2, CRS occurred in 91% of the 82 treated subjects. The most common CRS symptoms of any grade among the subjects with CRS were pyrexia (99%), followed by hypotension (60%), hypoxia (37%), chills (33%), tachycardia (27%) and headache (24%). Most of these events were Grade 1 or Grade 2. Grade 3 or higher CRS occurred in 15% of subjects. No subject had Grade 5 CRS.

Important Identified Risks	Risk-Benefit Impact
	In ZUMA-3, CRS occurred in 91% of the 100 treated subjects. The most common CRS symptom of any grade was pyrexia (90%), followed by hypotension (68%), sinus tachycardia (34%), chills (30%), hypoxia (27%), tachycardia (26%) and headache (20%). Grade 3 or higher CRS occurred in 25% of subjects. One subject had Grade 5 CRS and died on Day 6 due to multiple organ dysfunction syndrome secondary to CRS. HCPs should monitor patients for signs and symptoms of CRS and manage the risk as advised in the risk minimization measures. Proper monitoring and treatment are required to minimize the risk and to ensure an acceptable risk-benefit balance.
Cytopenias	Cytopenias are an expected consequence of treatment with brexucabtagene autoleucel. The lymphodepleting chemotherapy regimen (fludarabine and cyclophosphamide) is expected to cause bone marrow suppression {Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017a}. In ZUMA-2, percentages of subjects who experienced neutropenia, anemia and thrombocytopenia were 85%, 66%, and 70%, respectively. Grade 3 or higher neutropenia, anemia and thrombocytopenia occurred in 84%, 51% and 51% of subjects, respectively. No subject had a Grade 5 cytopenia. Subject incidence of Grade ≥3 cytopenias present on or after Day 30 included neutropenia 41%, anemia 18%, and thrombocytopenia 39%. In ZUMA-3, 56%, 50% and 48% of subjects experienced neutropenia, anemia and thrombocytopenia respectively; 56%, 46%, and 43% of these cases were Grade 3 or higher respectively. Subject incidence of Grade ≥3 cytopenias present on or after Day 30 included neutropenia 28%, anemia 12%, and thrombocytopenia 17%. HCPs should monitor blood counts. Proper monitoring and treatment are required to minimize the risk, especially prolonged cytopenias, to ensure an acceptable risk-benefit balance.
Infections	Lymphodepleting chemotherapy can cause neutropenia, which increases the risk of infections in subjects who will later receive brexucabtagene autoleucel therapy. Subjects with an active infection, including localized infections or inflammatory disease, should not be treated with brexucabtagene autoleucel therapy until these conditions resolve. In ZUMA-2, under the SOC of infections and infestations, 46 subjects (56%) had AEs of any grade. Of these subjects, 20 (24%) had Grade 3 events, 5 subjects (6%) had Grade 4 events and 1 subject (1%) had a Grade 5 event of staphylococcal bacteremia. In ZUMA-3, under the SOC of infections and infestations, 44 subjects (44%) had AEs of any grade. Of these subjects, 14 (14%) had Grade 3 events, 8 subjects (8%) had Grade 4 events and 8 subjects (8%) had a Grade 5 event (one subject each: herpes simplex viremia, fungal pneumonia, bacteremia, pneumonia, and septic shock; 3 subjects, sepsis). HCPs should monitor patients for signs and symptoms of infection, especially serious infection, before, during and after brexucabtagene autoleucel infusion and treat appropriately. Prophylactic antimicrobials should be administered according to standard institutional guidelines. Infections can be serious and proper monitoring and treatment are required to minimize the risk and to ensure an acceptable risk-benefit balance.

Important Identified Risks	Risk-Benefit Impact
Hypogammaglobulinemia	By causing B-cell depletion and hypogammaglobulinemia, brexucabtagene autoleucel therapy can predispose subjects to certain types of infections. In ZUMA-2, 13 subjects (16%) experienced hypogammaglobulinemia. Eleven of the 13 subjects received intravenous immunoglobulin therapy. In ZUMA-3, 7 subjects (7%) experienced hypogammaglobulinemia. Five of the 7 subjects received intravenous immunoglobulin therapy. HCPs should monitor immunoglobulin levels after treatment with brexucabtagene autoleucel and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement for recurrent infections.

Abbreviations: AE = adverse event; CRS = cytokine release syndrome; HCP = healthcare professional; SOC = system organ class.

SVII.1.3. Important Potential Risks

Table SVII. 3. Important Potential Risks

Important Potential Risks	Risk-Benefit Impact
Secondary malignancy	Secondary malignancy is a potential risk in studies of brexucabtagene autoleucel, as patients with ALL and NHL are known to be at risk for developing secondary malignancies {Ghimire 2014, Smeland 2016, Tward 2006}. In addition, there is a theoretical risk of secondary malignancy due to integration of the retroviral vector genome into the study subject's chromosomes. In ZUMA-2 and ZUMA-3, no subject developed a secondary malignancy attributable to brexucabtagene autoleucel therapy. Subjects in Kite clinical studies who have been treated with brexucabtagene autoleucel are being monitored long term for the development of secondary malignancy.
Immunogenicity	As with all biological therapeutics, there is a potential risk for immunogenicity with the use of brexucabtagene autoleucel. No brexucabtagene autoleucel related confirmed cases of immunogenicity were seen in ZUMA-2. In ZUMA-3, 2 subjects were confirmed to have antibodies to the anti-CD19 CAR after brexucabtagene autoleucel infusion. One of these subjects was confirmed to be antibody-positive after retreatment with brexucabtagene autoleucel. Antibodies can reduce efficacy and can cause safety issues such as anaphylaxis, CRS, infusion reactions etc. that could impact the risk-benefit balance. This risk of autoimmunity will be further evaluated. Based on the current evidence, a causal relationship between autoimmunity and brexucabtagene autoleucel cannot be confirmed and does not impact the risk-benefit balance.
RCR	Because a murine γ-retroviral vector is used in the production of brexucabtagene autoleucel, a potential risk exists for the presence of RCR. Subjects in Kite clinical studies who have been treated with brexucabtagene autoleucel are being monitored long term for the development of RCR. In ZUMA-2 and ZUMA-3, no subject tested positive for the presence of RCR. Blood samples for potential RCR testing by PCR are obtained from subjects at various time points during the first year after brexucabtagene autoleucel treatment and then annually for up to 15 years.

Important Potential Risks	Risk-Benefit Impact
TLS	Risk factors for TLS related to tumor size and expansion including bulky tumor, wide metastatic dispersal, and organ and/or bone marrow involvement. Tumor lysis syndrome risk is increased when a high potential for cell lysis exists; for example, in cases of high proliferation and tumor sensitivity to particular cytotoxic therapies, and highly intensive therapy. In ZUMA-2, 1 subject, a 56-year-old male, had worst Grade 3 nonserious TLS, which was assessed as being related to brexucabtagene autoleucel. In ZUMA-3, 2 subjects had a Grade 3 event of TLS. One event was assessed to be serious and unrelated to brexucabtagene autoleucel, and one was assessed as nonserious and related to brexucabtagene autoleucel. All subjects with significant malignancy burden and without a contraindication such as allergy should be started on prophylaxis (eg, allopurinol) as per institutional guidelines prior to initiation of lymphodepleting chemotherapy. Prophylaxis should be discontinued when the risk of tumor lysis has passed.
Aggravation of GvHD	There is a theoretical risk of aggravation of GvHD in patients who have previously undergone an allo-HSCT and then received donor derived engineered CAR T cells (from prior allo-HSCT donor) for their relapsed NHL. This theoretical risk is caused by engraftment of immunocompetent donor T lymphocytes in an immunologically compromised host and having histocompatibility differences with the donor, resulting in donor T cell activation against either the recipient MHC antigens or minor histocompatibility antigens {Liu 2017}. There were no cases of brexucabtagene autoleucel related GvHD or aggravation of GvHD in ZUMA-2 as patients with a history of allo-SCT were excluded per the protocol. In ZUMA-3 Phase 1, 3 subjects had GvHD, none of which were assessed as related to brexucabtagene autoleucel. In Phase 2, 1 subject who had undergone allo-HSCT prior to enrollment experienced worst Grade 2 GvHD, which was assessed as nonserious and related to brexucabtagene autoleucel. The evidence of GvHD or aggravation of GvHD after administration of engineered CAR T cells in patients with a previous allo-HSCT is limited. Patients who had undergone a prior allo-HSCT and then received donor derived CAR T cells (circulating cells in the patient from prior allo-HSCT donor) appeared to be at an increased risk of developing aggravation of GvHD or GvHD.

Abbreviations: ALL = acute lymphoblastic leukemia; allo-HSCT = allogeneic stem-cell transplant; CAR = chimeric antigen receptor; CAR T = chimeric antigen receptor T cells; CD19 = cluster of differentiation; CRS = cytokine release syndrome; GvHD = graft vs host disease; MHC = major histocompatibility complex; NHL = non-Hodgkin lymphoma; PCR = polymerase chain reaction; RCR = replication competent retrovirus; TLS = tumor lysis syndrome.

SVII.1.3.1. Missing Information

Table SVII. 4. Missing Information

Missing Information	Risk-Benefit Impact
New occurrence or exacerbation of an autoimmune disorder	Patients with autoimmune disorders were excluded from enrollment in the clinical development program and therefore the safety of use of brexucabtagene autoleucel in this population is considered missing information. A new occurrence or exacerbation of preexisting autoimmune disorder is a theoretical risk. Thus, the risks of use in this population cannot be defined.
Long-term safety	Long-term safety of brexucabtagene autoleucel is not yet known. The safety profile of long-term effects will be derived from routine and additional pharmacovigilance activities including a registry.

SVII.2. New Safety Concerns and Reclassification with a Submission of an updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risks

Table SVII. 5. Important Identified Risk: Serious Neurologic Events including Cerebral Edema

Important Identified Risk:	Serious Neurologic Events including Cerebral Edema
Potential mechanisms	Increase in the level of inflammatory cytokines (eg, IL-1, IL-6 and GM-CSF) after CAR T cell administration may lead to macrophage and endothelial activation and blood-brain barrier disruption {Siegler 2020}.
Evidence source and strength of evidence	Serious neurologic adverse events were reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.
Characterization of the risk	**Clinical trials** **ZUMA-2 Cohort 1 (as of 24 July 2021)** Forty-three subjects (63%) had at least 1 neurologic event of any grade, 15 subjects (22%) had worst Grade 3 neurologic events, 6 subjects (9%) had worst Grade 4 neurologic events, and no subject had a Grade 5 neurologic event. One subject had Grade 4 cerebral edema. The most common neurologic events of any grade were tremor (24 subjects, 35%), encephalopathy (18 subjects, 26%), and confusional state (14 subjects, 21%). The most common Grade 3 or higher neurologic events were encephalopathy (12 subjects, 18%), confusional state (8 subjects, 12%), and aphasia (3 subjects, 4%).

Important Identified Risk:	Serious Neurologic Events including Cerebral Edema

The median time to onset of a neurologic event was 7 days (range: 1 to 32 days) after the brexucabtagene autoleucel infusion. As of the data cutoff date, neurologic events had resolved in 40 of 43 subjects; the median duration of these neurologic events was 15 days (range: 1 to 708 days). Of the remaining 3 subjects with unresolved neurologic events, 1 subject had ongoing neurologic events at the data cutoff date, and 2 subjects had neurologic events that were unresolved at death.

In Cohort 1, 22 subjects (32%) had serious neurologic events of any grade. The most common serious neurologic event was encephalopathy (12 subjects, 18%), followed by confusional state (5 subjects, 7%) and aphasia and immune effector cell associated neurotoxicity syndrome (3 subjects each, 4%).

ZUMA-3 (as of 23 January 2024)

In ZUMA-3, 69% of subjects had neurologic events, with 32 % with worst grade ≥ 3. Serious neurologic events reported in ZUMA-3 are summarized below.

Subject Incidence of Treatment-emergent Serious Adverse Events of Interest - Neurologic Events in ZUMA-3 (Phase 1 and Phase 2 Safety Analysis Set, N = 100)

MedDRA Preferred Term, n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with any serious neurologic event	35 (35)	1 (1)	7 (7)	22 (22)	4 (4)	1 (1)
Encephalopathy	15 (15)	0 (0)	2 (2)	9 (9)	4 (4)	0 (0)
Aphasia	7 (7)	0 (0)	1 (1)	6 (6)	0 (0)	0 (0)
Confusional state	5 (5)	0 (0)	4 (4)	1 (1)	0 (0)	0 (0)
Seizure	5 (5)	1 (1)	1 (1)	3 (3)	0 (0)	0 (0)
Paraparesis	2 (2)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Brain herniation	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Brain oedema	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Delirium	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Disorientation	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Immune effector cell-associated neurotoxicity syndrome	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Mental status changes	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Monoplegia	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Restlessness	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Status epilepticus	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)

Data cutoff date = 23Jul2023
Abbreviations: AE, adverse event; CAR, chimeric antigen receptor; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA,
Medical Dictionary for Regulatory Activities.
Note: Preferred terms are sorted in descending order of total frequency in the 'Any' column.
Adverse events are coded using MedDRA version 26.0 and graded using CTCAE 4.03.
Multiple incidences of the same AE in one subject are counted once at the highest grade for that subject.
Treatment-emergent AEs include all AEs with onset on or after initiation of the KTE-X19 infusion. For subjects who underwent retreatment with
KTE-X19, the AEs occurring during the retreatment period are not included.
Neurologic events are identified based on a modification of criteria proposed by Topp and colleagues {Topp 2015}.
Data Source: ADSL, ADAE Program Name: t_ne Output Generated: 20230919T11:31

Impact on quality of life

AEs such as encephalopathy, confusional state, aphasia, lethargy, mental status change, seizures, brain edema, somnolence and tremor have significant impact on the patient's quality of life; they can cause severe distress, impair ability to read, write or communicate intelligibly and, if serious, can be life-threatening requiring urgent intervention and mechanical ventilation. Severe cases, including cerebral edema, may lead to death.

Post-marketing experience (cumulative to 23 January 2024)

Serious Neurologic Events including Cerebral Edema reported in the Post-marketing Setting (Cumulative to 23 January 2024)

Category		Value
Total number of Cases		394
Total number of Events		588
	Serious	473
	Non-Serious	115
Event Outcomes		
	Fatal	33
	Lost to follow-up	0
	Not Resolved	42
	Resolved	206
	Resolved with Sequelae	1
	Resolving	22
	Unknown	231
Time to event onset range (median) days		0-68 (7)
Events by PT (descending order)		
	Immune effector cell-associated neurotoxicity syndrome	282
	Neurotoxicity	83
	Tremor	32
	Confusional state	29
	Encephalopathy	22
	Memory impairment	16
	Aphasia	15
	Somnolence	13
	Agitation	10
	Depressed level of consciousness	8
	Seizure	8
	Brain oedema	7
	Nervous system disorder	5
	Unresponsive to stimuli	5
	Loss of consciousness	4
	Neurological symptom	4
	Cognitive disorder	3
	Delirium	3
	Disorientation	3
	Dysgraphia	3

Important Identified Risk:	Serious Neurologic Events including Cerebral Edema
	<table><tr><td></td><td>Epilepsy</td><td>3</td></tr><tr><td></td><td>Hallucination, visual</td><td>3</td></tr><tr><td></td><td>Lethargy</td><td>3</td></tr><tr><td></td><td>Mental status changes</td><td>3</td></tr><tr><td></td><td>Paraesthesia</td><td>3</td></tr><tr><td></td><td>Speech disorder</td><td>3</td></tr></table> Abbreviations: PT = preferred term.
Risk groups or risk factors	Female patients and subjects with higher ECOG performance status had a higher incidence of neurologic events.
Preventability	Tecartus must be administered at a qualified treatment centre. It is recommended patients are monitored daily for the first 7 days following infusion for signs and symptoms of potential neurologic events. It is recommended physicians consider hospitalisation for the first 7 days post infusion or at the first signs/symptoms of neurologic events. After the first 7 days following infusion, the patient is to be monitored at the physician's discretion. Patients must remain within proximity (within 2 hours of travel) of the qualified treatment center for at least 4 weeks following infusion and seek immediate medical attention should signs or symptoms of neurologic adverse reactions/ICANS occur. Patients who experience Grade 2 or higher neurologic toxicity/ICANS must be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive-care supportive therapy for severe or life-threatening neurologic toxicity/ICANS. Non-sedating, anti-seizure medicines are be considered as clinically indicated for Grade 2 or higher adverse reactions. Treatment algorithms have been developed to ameliorate the neurologic adverse reactions experienced by patients on Tecartus. These include the use of tocilizumab (if concurrent CRS) and/or corticosteroids for moderate, severe, or life-threatening neurologic adverse reactions as summarised in the SmPC. Due to the potential for neurologic events, including altered mental status or seizures, patients must not drive or operate heavy or potentially dangerous machines until at least 8 weeks after infusion or until resolution of neurologic adverse reactions.
Impact on the benefit-risk balance of the product	Routine and additional pharmacovigilance activities will further characterize the risk of serious neurologic events with respect to number of reports, seriousness, outcome, and risk factors and that the data is consistent with the information already known for this risk. The safe use of brexucabtagene autoleucel will be enhanced through routine risk minimization measures and supported by aRMMs such as HCP educational material, PAC and Controlled distribution program. The risk will be mitigated by these measures such that the benefit risk for the product, considering the seriousness of the indication, is positive.
Public health impact	Minimal due to the relatively low number of people affected by the indication.

Abbreviations: aRMMs = additional risk minimization measures; CAR T = chimeric antigen receptor T cells; CRS = cytokine release syndrome; ECOG = Eastern Cooperative Oncology Group; EU = European Union; GM-CSF = granulocyte-macrophage colony-stimulating factor; HCP = healthcare professional; ICANS = immune effector cell-associated neurotoxicity syndrome; IL-1 = interleukin 1; IL-6 = interleukin 6; PAC = patient alert card.

Table SVII. 6. Important Identified Risk: Cytokine Release Syndrome

Important Identified Risk:	Cytokine Release Syndrome
Potential mechanisms	Cytokines, chemokines and effector molecules implicated in CRS may be directly produced by the infused CAR T cells, as well as other immune cells such as CD14+ myeloid cells that might produce large amounts of these analytes. Correlative analyses were performed for Cohort 1 only. Peak blood levels of anti CD19 CAR T cells were higher for subjects with higher grades of CRS. The median peak level of anti-CD19 CAR T cells was 4.8-fold higher for subjects with Grade 3 or higher CRS compared with subjects with Grade 2, Grade 1, or no CRS (273.72 versus 57.07 cells/μL; nominal p = 0.0163). Of the 17 key analytes statistically evaluated, the median peak serum levels for the following analytes were higher (nominal Wilcoxon rank-sum p value ≤ 0.05) among subjects who experienced Grade 3 or higher CRS versus Grade 2, Grade 1, or no CRS after infusion of brexucabtagene autoleucel: ferritin, granzyme B, IL-2Rα, IL-6, IL-8, IL-10, IL-15, perforin, TNF-α and GM-CSF {Wang 2019}. A wide variety of cytokines and chemokines including IL-6, interferon-γ, TNF-α, IL-2, IL-2Rα, IL-1 receptor antagonist, IL-8, and IL-10 are elevated in the serum of patients experiencing fever, tachycardia, hypotension, and other toxicities after CAR T cell infusions {Brudno 2016}. The associations of CRS with several of these cytokines and chemokines is likely related to their known functional activities. IL-6 and TNF-α mediate vascular permeability, hypotension, fever, and tissue damage {Sprague 2009}; chemokines such as IL-8 trigger mobilization and redistribution of activated immune cells throughout the body {Griffith 2014}; and IL-1ra and IL-2Rα are indicative of macrophage and general immune activation {Ravelli 2012}. Levels of these cytokines decreased 1 month post CAR T cell infusion, a finding generally consistent with the timing and reversibility of CRS.
Evidence source and strength of evidence	CRS was reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.
Characterization of the risk	**Clinical trials** **ZUMA-2 Cohort 1 (as of 24 July 2021)** In total, 62 subjects (91%) had CRS; the majority of subjects had worst Grade 1 (20 subjects, 29%) or worst Grade 2 (32 subjects, 47%) CRS. Eight subjects (12%) had worst Grade 3 CRS, and 2 subjects (3%) had worst Grade 4 CRS. No subject had Grade 5 CRS. The most common CRS symptoms of any grade were pyrexia (62 subjects, 100%), hypotension (35 subjects, 56%), and hypoxia (23 subjects, 37%). The most common worst Grade 3 or higher CRS symptoms were hypotension (15 subjects, 24%), hypoxia (12 subjects, 19%), and pyrexia (7 subjects, 11%). Among the 62 subjects who had CRS, the median time to onset was 2 days (range: 1 to 13 days) after the brexucabtagene autoleucel infusion. As of the data cutoff date, CRS had resolved in all subjects. The median duration of CRS was 11 days (range: 1 to 50 days). **ZUMA-3 (as of 23 January 2024)** In ZUMA-3, CRS occurred in 91% of the 100 treated subjects, with 25% worst grade ≥3.

Subject Incidence of Treatment -emergent Serious Adverse Events of Interest – Symptoms of CRS in ZUMA-3 (Phase 1 and Phase 2 Safety Analysis Set, N = 100)

Event, n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with any CRS	39 (39)	19 (19)	47 (47)	15 (15)	9 (9)	1 (1)
Hypotension	28 (28)	0 (0)	7 (7)	15 (15)	6 (6)	0 (0)
Pyrexia	18 (18)	0 (0)	8 (8)	7 (7)	3 (3)	0 (0)
Hypoxia	11 (11)	0 (0)	0 (0)	5 (5)	6 (6)	0 (0)
Tachycardia	5 (5)	0 (0)	4 (4)	1 (1)	0 (0)	0 (0)
Dyspnoea	3 (3)	0 (0)	2 (2)	1 (1)	0 (0)	0 (0)
Disseminated intravascular coagulation	2 (2)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)
Fatigue	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Acute respiratory distress syndrome	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Acute respiratory failure	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Chills	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhoea	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Haemophagocytic lymphohistiocytosis	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Hypervolaemia	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Multiple organ dysfunction syndrome	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Pulmonary alveolar haemorrhage	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Pulseless electrical activity	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Rash	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Respiratory failure	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Tachypnoea	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)

Data cutoff date = 23Jul2023
Abbreviations: CRS, cytokine release syndrome; TEAE, treatment-emergent adverse event.
Note: Preferred terms are sorted in descending order of total frequency in the 'Any' column.
Adverse events are coded using MedDRA version 26.0 and graded using CTCAE 4.03.
Multiple incidences of the same AE in one subject are counted once at the highest grade for that subject.
Treatment-emergent AEs include all AEs with onset on or after initiation of the KTE-X19 infusion. For subjects who underwent retreatment with
KTE-X19, the AEs occurring during the retreatment period are not included.
Data Source: ADSL, ADAE Program Name: t_crs_ser Output Generated: 20230919T11:30

Impact on quality of life

AEs, including fever, malaise, fatigue, anorexia, myalgia, arthralgia, nausea, vomiting, diarrhea, headache, skin rashes, tachypnea, hypoxemia, tachycardia, hypotension, increased or decreased cardiac output, renal impairment, elevated transaminases and bilirubin can cause severe distress and require medical intervention. In the short-term CRS will impact the patient’s quality of life although this is short lived and likely to be confined to the period of hospitalization, with limited long-term effects. In severe cases, CRS-related SAEs may be associated with death.

<table>
<tr><td>Important Identified Risk:</td><td>Cytokine Release Syndrome</td></tr>
<tr><td></td><td>Post-marketing experience (cumulative to 23 January 2024)
<table>
<tr><th colspan="3">CRS Events reported in the Post-marketing Setting (Cumulative to 23 January 2024)</th></tr>
<tr><th>Category</th><th></th><th>Value</th></tr>
<tr><td>Total number of Cases</td><td></td><td>449</td></tr>
<tr><td>Total number of Events</td><td></td><td>458</td></tr>
<tr><td></td><td>Serious</td><td>458</td></tr>
<tr><td></td><td>Non-Serious</td><td>0</td></tr>
<tr><td>Events Grade 3 or higher</td><td></td><td>78</td></tr>
<tr><td>Event Outcomes</td><td></td><td></td></tr>
<tr><td></td><td>Fatal</td><td>18</td></tr>
<tr><td></td><td>Lost to follow-up</td><td>0</td></tr>
<tr><td></td><td>Not Resolved</td><td>16</td></tr>
<tr><td></td><td>Resolved</td><td>183</td></tr>
<tr><td></td><td>Resolved with Sequelae</td><td>1</td></tr>
<tr><td></td><td>Resolving</td><td>9</td></tr>
<tr><td></td><td>Unknown</td><td>194</td></tr>
<tr><td>Time to event onset range (median) days</td><td></td><td>0-20 (4)</td></tr>
</table>
Abbreviations: CRS = cytokine release syndrome.</td></tr>
<tr><td>Risk groups or risk factors</td><td>A higher disease burden, older age, organ dysfunction and female gender were associated with a higher rate of CRS.</td></tr>
<tr><td>Preventability</td><td>Tecartus must be administered at qualified treatment centers by a physician with experience in the treatment of hematological malignancies and trained for administration and management of patients treated with Tecartus. It is recommended patients are monitored daily for the first 7 days following infusion for signs and symptoms of potential CRS. It is recommended physicians consider hospitalisation for the first 7 days post infusion or at the first signs/symptoms of CRS. After the first 7 days following the infusion, the patient is to be monitored at the physician’s discretion. Patients must remain within proximity (within 2 hours of travel) of a qualified treatment centre for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS occur. Patients must be closely monitored for signs or symptoms of high fever, hypotension, hypoxia, chills, tachycardia and headache. CRS is to be managed at the physician’s discretion, based on the patient’s clinical presentation and according to the CRS management algorithm provided in the SmPC.
At least 1 dose per patient of tocilizumab must be on site and available for administration prior to Tecartus infusion. The qualified treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, the treatment center must have access to suitable alternative measures instead of tocilizumab to treat CRS.
Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients on Tecartus. These include the use of tocilizumab or tocilizumab and corticosteroids.</td></tr>
</table>

Important Identified Risk:	Cytokine Release Syndrome
	Patients who experience Grade 2 or higher CRS (e.g., hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) must be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive-care supportive therapy. Patients with medically significant cardiac dysfunction must be managed by standards of critical care and measures such as echocardiography is to be considered. TNF antagonists are not recommended for management of Tecartus-associated CRS.
Impact on the benefit-risk balance of the product	Routine and additional pharmacovigilance activities will further characterize the risk of CRS with respect to number of reports, seriousness, outcome, and risk factors and determine whether the data is consistent with the information already known for this risk. The safe use of brexucabtagene autoleucel will be enhanced through routine risk minimization measures and supported by aRMMs such as HCP educational materials, PAC, and controlled distribution plan. The risk will be mitigated by these measures such that the benefit-risk for the product, considering the seriousness of the indication, is positive.
Public health impact	Minimal due to the relatively low number of people affected by the indication.

Abbreviations: AE = adverse events; aRMMs = additional risk minimization measures; CAR T = chimeric antigen receptor T cells; $CD14^+$ = cluster of differentiation 14-positive cells; CD19 = cluster of differentiation 19; CRS = cytokine release syndrome; GM-CSF = granulocyte-macrophage colony-stimulating factor; HCP = healthcare professional; IL-1 = interleukin 1; IL-1Rα = interleukin 1 receptor α; IL-2Rα = interleukin 2 receptor α; IL-6 = interleukin 6; IL-8 = interleukin 8; IL-10 = interleukin 10; IL-15 = interleukin 15; PAC = patient alert card; SAE = serious adverse event; SmPC = summary of product characteristics; TNFα = tumor necrosis factor alpha.

Table SVII. 7. Important Identified Risk: Cytopenias

Important Identified Risk:	Cytopenias
Potential mechanisms	Cytopenias, especially prolonged cytopenias, is a well-known risk associated with conditioning chemotherapy. However, there is often difficulty in determining the etiology of cytopenias occurring after CAR T-cell infusions, because chemotherapy that causes cytopenias is normally given before CAR T-cell infusions. Prior treatment with chemotherapeutic agents and underlying disease can also contribute to the occurrence of cytopenias. Patients not receiving conditioning chemotherapy have also experienced cytopenias following CAR T-cell infusion, demonstrating that the CAR T cells cause myelosuppression by a cytokine-mediated mechanism or some other mechanism {Brudno 2016}.
Evidence source and strength of evidence	Cytopenias were reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.
Characterization of the risk	**Clinical trials** **ZUMA-2 Cohort 1 (as of 24 July 2021)** Fifty subjects (74%) had thrombocytopenia AEs, and 36 subjects (53%) had worst Grade 3 or higher thrombocytopenia AEs. Fifty-nine subjects (87%) had neutropenia AEs, and 58 subjects (85%) had worst Grade 3 or higher neutropenia AEs. Forty-seven subjects (69%) had anemia AEs of any grade, 36 subjects (53%) had worst Grade 3 anemia AEs, and no subject had worst Grade 4 anemia. Grade 3 and Grade 4 thrombocytopenia AEs were present on or after Day 30 in 8 subjects (12%) and 20 subjects (29%), respectively. Eleven subjects (16%) had Grade 3 and 20 subjects (29%) had Grade 4 neutropenia AEs that were present on or

Important Identified Risk:	Cytopenias

after Day 30. Fourteen subjects (21%) had Grade 3 anemia AEs on or after Day 30, and no subject had Grade 4 anemia on or after Day 30.

ZUMA-3 (as of 23 January 2024)

Forty eight (48) percent of participants had thrombocytopenia, 56% had neutropenia and 50% had anemia.

Subject Incidence of Treatment-emergent Adverse Events of Interest - Thrombocytopenia, Neutropenia and Anemia in ZUMA-3 (Phase 1 and Phase 2, Safety Analysis Set, N = 100)

	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with any thrombocytopenia, neutropenia, or anemia	78 (78)	0 (0)	0 (0)	22 (22)	56 (56)	0 (0)
Subjects with any thrombocytopenia	48 (48)	3 (3)	2 (2)	5 (5)	38 (38)	0 (0)
Platelet count decreased	35 (35)	2 (2)	0 (0)	5 (5)	28 (28)	0 (0)
Thrombocytopenia	14 (14)	1 (1)	2 (2)	0 (0)	11 (11)	0 (0)
Subjects with any neutropenia	56 (56)	0 (0)	0 (0)	20 (20)	36 (36)	0 (0)
Neutrophil count decreased	27 (27)	0 (0)	0 (0)	5 (5)	22 (22)	0 (0)
Febrile neutropenia	17 (17)	0 (0)	0 (0)	17 (17)	0 (0)	0 (0)
Neutropenia	17 (17)	0 (0)	0 (0)	3 (3)	14 (14)	0 (0)
Subjects with any anemia	50 (50)	0 (0)	4 (4)	44 (44)	2 (2)	0 (0)
Anaemia	50 (50)	0 (0)	4 (4)	44 (44)	2 (2)	0 (0)

Data cutoff date = 23Jul2023
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standard MedDRA query
Note: Preferred terms are sorted in descending order of total frequency in the 'Any' column within each category.
Adverse events are coded using MedDRA version 26.0 and graded using CTCAE 4.03.
Multiple incidences of the same AE in one subject are counted once at the highest grade for that subject.
Thrombocytopenia is identified using SMQ haematopoietic thrombocytopenia (narrow search).
Neutropenia is identified using MedDRA search terms pre-specified by Kite.
Anemia is identified with SMQ haematopoietic erythropenia (broad search).
Data Source: ADSL, ADAE Program Name: t_pt_sev_eoi Output Generated: 20230919T11:32

Post-marketing experience (cumulative to 23 January 2024)

Cytopenia Events reported in the Postmarketing Setting (Cumulative to 23 January 2024)

Category		Value
Total number of Cases		63
Total number of Events		84
	Serious	80
	Non-Serious	4

<table>
<tr><td>Important Identified Risk:</td><td>Cytopenias
<table>
<tr><td>Event Outcomes</td><td></td><td></td></tr>
<tr><td></td><td>Fatal</td><td>3</td></tr>
<tr><td></td><td>Lost to follow-up</td><td>0</td></tr>
<tr><td></td><td>Not Resolved</td><td>14</td></tr>
<tr><td></td><td>Resolved</td><td>21</td></tr>
<tr><td></td><td>Resolved with Sequelae</td><td>0</td></tr>
<tr><td></td><td>Resolving</td><td>8</td></tr>
<tr><td></td><td>Unknown</td><td>36</td></tr>
<tr><td>Time to event onset range (median) days</td><td></td><td>28-77 (61)</td></tr>
<tr><td>Events by PT (descending order)</td><td></td><td></td></tr>
<tr><td></td><td>Pancytopenia</td><td>18</td></tr>
<tr><td></td><td>Neutropenia</td><td>17</td></tr>
<tr><td></td><td>Thrombocytopenia</td><td>14</td></tr>
<tr><td></td><td>Cytopenia</td><td>13</td></tr>
<tr><td></td><td>Febrile neutropenia</td><td>9</td></tr>
<tr><td></td><td>Anaemia</td><td>2</td></tr>
<tr><td></td><td>Bone marrow failure</td><td>2</td></tr>
<tr><td></td><td>Neutrophil count decreased</td><td>2</td></tr>
<tr><td></td><td>Platelet count decreased</td><td>2</td></tr>
</table>
Abbreviations: PT = preferred term.</td></tr>
<tr><td>Risk groups or risk factors</td><td>Prior exposure to chemotherapy or radiation.</td></tr>
<tr><td>Preventability</td><td>Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Tecartus infusion and must be managed according to standard guidelines.
Blood counts must be monitored after Tecartus infusion.</td></tr>
<tr><td>Impact on the benefit-risk balance of the product</td><td>Routine and additional pharmacovigilance activities will further characterize the risk of cytopenias with respect to number of reports, seriousness, outcome, and risk factors and to determine whether the data is consistent with the information already known for this risk. The safe use of brexucabtagene autoleucel will be enhanced through routine risk minimization measures. The risk will be mitigated by these measures such that the benefit-risk for the product, considering the seriousness of the indication is positive.</td></tr>
<tr><td>Public health impact</td><td>Minimal due to the relatively low number of people affected by the indication.</td></tr>
</table>

Abbreviations: AE = adverse event; CAR T = chimeric antigen receptor T cells.

Table SVII. 8. Important Identified Risk: Infections

Important Identified Risk:	Infections
Potential mechanisms	Prolonged B-cell aplasia is an expected toxicity of anti-CD19 CAR T-cells due to their cytotoxic activity towards CD19 expressing B-cells. In addition, infections could be the result of chemotherapy-induced cytopenias and immunosuppression, including depletion of B-cells and T cells and hypogammaglobulinemia, which is often given before CAR T-cell infusions. However, patients not receiving conditioning chemotherapy have also experienced cytopenias following CAR T-cell infusion, demonstrating that the CAR T cells cause myelosuppression by a cytokine-mediated mechanism or some other mechanism {Brudno 2016}.
Evidence source and strength of evidence	Infections were reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.
Characterization of the risk	**Clinical trials** **ZUMA-2 Cohort 1 (as of 24 July 2021)** Within the SOC of infections and infestations, 38 subjects (56%) had AEs of any grade, and 25 subjects (37%) had worst Grade 3 or higher AEs. Two subjects had Grade 5 infections. The most common PTs within this SOC were pneumonia (13 subjects, 19%), upper respiratory infections (10 subjects, 15%), and sinusitis (6 subjects, 9%). One subject died of COVID-19, which was reported as a cause of death and not an AE. In Cohort 1, 11 subjects (16%) had bacterial infections of any grade; 4 subjects (6%) had worst Grade 3 events and no subject had a worst Grade 4 event. One subject had a Grade 5 staphylococcal bacteremia and 1 subject had a Grade 5 salmonella bacteremia. The most common bacterial infections of any grade were cellulitis and staphylococcal bacteremia (2 subjects each, 3%). All other bacterial infections occurred in 1 subject each. In Cohort 1, 11 subjects (16%) had a viral infection of any grade, and 3 subjects (4%) had a worst Grade 3 viral infection. No subject had a viral infection of worst Grade 4 or Grade 5. The most common viral infections of any grade were influenza (4 subjects, 6%), herpes zoster (3 subjects, 4%) and viral upper respiratory infections (2 subjects, 3%); all other viral infections occurred in 1 subject each (1%). One subject died of COVID-19, which was reported as a cause of death and not an AE. Two subjects (3%) had opportunistic infections of any grade in Cohort 1; these infections were worst Grade 2. Two types of opportunistic infections were reported: cytomegalovirus infection reactivation and cytomegalovirus viremia (1 subject each, 1%). In Cohort 1, 32 subjects (47%) had unspecified pathogen infections; these infections were Grade 3 or higher in 20 subjects (29%). No subject had a Grade 5 infection in this category. The most common infections of any grade in this category were pneumonia (13 subjects, 19%), upper respiratory tract infections (10 subjects, 15%), and sinusitis (6 subjects, 9%). **ZUMA-3 (as of 23 January 2024)** In ZUMA-3, 42% had any TE infection with 25% a serious TE infection. Infections by type are presented below:

Bacterial infections:

Subject Incidence of Treatment-emergent Adverse Events of Interest – Bacterial Infections (Phase 1 and Phase 2, Safety Analysis Set, N = 100)

MedDRA Preferred Term, n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with bacterial infection	12 (12)	3 (3)	3 (3)	4 (4)	2 (2)	0 (0)
Clostridium difficile infection	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Enterococcal bacteraemia	2 (2)	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)
Escherichia bacteraemia	2 (2)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)
Cellulitis	1 (1)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)
Cellulitis of male external genital organ	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Clostridial infection	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Clostridium difficile colitis	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Escherichia infection	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Escherichia sepsis	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Folliculitis	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Pseudomonas infection	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Staphylococcal bacteraemia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Staphylococcal infection	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Wound infection staphylococcal	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)

Data cutoff date = 23Jul2023
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; HLGT, high-level group term; MedDRA,
Medical Dictionary for Regulatory Activities.
Note: Preferred terms are sorted in descending order of total frequency in the 'Any' column.
Adverse events are coded using MedDRA version 26.0 and graded using CTCAE 4.03.
Multiple incidences of the same AE in one subject are counted once at the highest grade for that subject.
Treatment-emergent AEs include all AEs with onset on or after initiation of the KTE-X19 infusion. For subjects who underwent retreatment with
KTE-X19, the AEs occurring during the retreatment period are not included.
Bacterial infection search strategy used bacterial infectious disorders (HLGT) and chlamydial infectious disorders (HLGT).
Data Source: ADSL, ADBASE, ADAE Program Name: t_ae_ptsev Output Generated: 20230919T11:28

Viral infections:

Subject Incidence of Treatment-emergent Adverse Events of Interest - Viral Infections (Phase 1 and Phase 2, Safety Analysis Set, N = 100)

MedDRA Preferred Term, n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with any viral infection	6 (6)	0 (0)	2 (2)	3 (3)	0 (0)	1 (1)
Cytomegalovirus viraemia	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Herpes simplex	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Herpes simplex viraemia	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)

Important Identified Risk:	**Infections**

Influenza	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Pneumonia respiratory syncytial viral	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Respiratory syncytial virus infection	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Rhinovirus infection	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)

Data cutoff date = 23Jul2023
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; HLGT, high-level group term; MedDRA,
Medical Dictionary for Regulatory Activities.
Note: Preferred terms are sorted in descending order of total frequency in the 'Any' column.
Adverse events are coded using MedDRA version 26.0 and graded using CTCAE 4.03.
Multiple incidences of the same AE in one subject are counted once at the highest grade for that subject.
Treatment-emergent AEs include all AEs with onset on or after initiation of the KTE-X19 infusion. For subjects who underwent retreatment with
KTE-X19, the AEs occurring during the retreatment period are not included.
Viral infection search strategy used viral infectious disorders (HLGT).
Data Source: ADSL, ADBASE, ADAE Program Name: t_ae_ptsev Output Generated: 20230919T11:28

Other infections:

Subject Incidence of Treatment-emergent Adverse Events of Interest – Opportunistic Infections (Phase 1 and Phase 2, Safety Analysis Set, N = 100)

MedDRA Preferred Term, n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with any opportunistic infection	6 (6)	0 (0)	1 (1)	3 (3)	0 (0)	2 (2)
Cytomegalovirus viraemia	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Herpes simplex viraemia	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Osteomyelitis fungal	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Pneumocystis jirovecii pneumonia	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Pneumonia fungal	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Sinusitis fungal	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)

Data cutoff date = 23Jul2023
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; HLGT, high-level group term; MedDRA,
Medical Dictionary for Regulatory Activities.
Note: Preferred terms are sorted in descending order of total frequency in the 'Any' column.
Adverse events are coded using MedDRA version 26.0 and graded using CTCAE 4.03.
Multiple incidences of the same AE in one subject are counted once at the highest grade for that subject.
Treatment-emergent AEs include all AEs with onset on or after initiation of the KTE-X19 infusion. For subjects who underwent retreatment with
KTE-X19, the AEs occurring during the retreatment period are not included.
Opportunistic infection search strategy used fungal infectious disorders (HLGT) and mycobacterial infectious disorders (HLGT).
Data Source: ADSL, ADBASE, ADAE Program Name: t_ae_ptsev Output Generated: 20230919T11:28

<table>
<tr><td>Important Identified Risk:</td><td>Infections</td></tr>
<tr><td></td><td>Post-marketing experience (cumulative to 23 January 2024)
Infection Events reported in the Postmarketing Setting (Cumulative to 23 January 2024)
<table>
<tr><th>Category</th><th></th><th>Value</th></tr>
<tr><td>Total number of Cases</td><td></td><td>62</td></tr>
<tr><td>Total number of Events</td><td></td><td>89</td></tr>
<tr><td></td><td>Serious</td><td>74</td></tr>
<tr><td></td><td>Non-Serious</td><td>15</td></tr>
<tr><td>Event Outcomes</td><td></td><td></td></tr>
<tr><td></td><td>Fatal</td><td>37</td></tr>
<tr><td></td><td>Lost to follow-up</td><td>0</td></tr>
<tr><td></td><td>Not Resolved</td><td>6</td></tr>
<tr><td></td><td>Resolved</td><td>6</td></tr>
<tr><td></td><td>Resolved with Sequelae</td><td>0</td></tr>
<tr><td></td><td>Resolving</td><td>1</td></tr>
<tr><td></td><td>Unknown</td><td>33</td></tr>
<tr><td>Events by PT (descending order)</td><td></td><td></td></tr>
<tr><td></td><td>COVID-19</td><td>10</td></tr>
<tr><td></td><td>Sepsis</td><td>10</td></tr>
<tr><td></td><td>Infection</td><td>9</td></tr>
<tr><td></td><td>Septic shock</td><td>6</td></tr>
<tr><td></td><td>Mucormycosis</td><td>4</td></tr>
<tr><td></td><td>Urinary tract infection</td><td>3</td></tr>
<tr><td></td><td>Aspergillus infection</td><td>2</td></tr>
<tr><td></td><td>Cytomegalovirus infection reactivation</td><td>2</td></tr>
<tr><td></td><td>Endocarditis</td><td>2</td></tr>
<tr><td></td><td>Pneumonia</td><td>2</td></tr>
<tr><td></td><td>Rhinovirus infection</td><td>2</td></tr>
</table>
Abbreviations: PT = preferred term.</td></tr>
<tr><td>Risk groups or risk factors</td><td>Patient factors: Underlying immune deficiencies, medical comorbidities, past infections, poor nutritional status, and psychological stress.
Additive or synergistic factors: Surgery, radiation, immunosuppressant therapies, antimicrobial use, and invasive procedures.</td></tr>
<tr><td>Preventability</td><td>Infusion must be delayed if a patient has any active uncontrolled infection. Patients must be monitored for signs and symptoms of infection before, during, and after infusion and treated appropriately. Prophylactic anti-microbials should be administered according to standard institutional guidelines.
Screening for HBV, HCV, and HIV should be performed before collection of cells for manufacturing of brexucabtagene autoleucel.</td></tr>
</table>

Important Identified Risk:	Infections
Impact on the benefit-risk balance of the product	Routine and additional pharmacovigilance activities will further characterize the risk of infections with respect to number of reports, seriousness, outcome, and risk factors and determine if data is consistent with the information already known for this risk. The safe use of brexucabtagene autoleucel will be enhanced through routine risk minimization measures. The risk will be mitigated by these measures such that the benefit-risk for the product, considering the seriousness of the indication, is positive.
Public health impact	Minimal due to the relatively low number of people affected by the indication.

Abbreviations: AE = adverse events; CAR T = chimeric antigen receptor T cells; CD19 = cluster of differentiation; HBV = hepatitis B virus; HCV = hepatitis C virus; PT = preferred term; SOC = system organ class.

Table SVII. 9. Important Identified Risk: Hypogammaglobulinemia

Important Identified Risk:	Hypogammaglobulinemia
Potential mechanisms	B-cell aplasia is an expected consequence of treatment with brexucabtagene autoleucel which may lead to hypogammaglobinemia.
Evidence source and strength of evidence	Hypogammaglobinemia was reported in clinical trials in patients treated with other CAR T therapies.
Characterization of the risk	**Clinical trials** **ZUMA-2 Cohort 1 (as of 24 July 2021)** In Cohort 1, 14 subjects (21%) had hypogammaglobulinemia. **ZUMA-3 (as of 23 July 2024)** In ZUMA-3, 7 subjects (7%) experienced hypogammaglobulinemia. Five of the 7 subjects received intravenous immunoglobulin therapy. **Post-marketing experience (cumulative to 23 January 2024)**

Infection Events reported in the Postmarketing Setting (Cumulative to 23 January 2024)

Category		Value
Total number of Cases		2
Total number of Events		3
	Serious	2
	Non-Serious	1
Event Outcomes		
	Fatal	0
	Lost to follow-up	0
	Not Resolved	2
	Resolved	0
	Resolved with Sequelae	0
	Resolving	0
	Unknown	1
Events by PT (descending order)		
	Hypogammaglobulinaemia	2
	Immunoglobulins decreased	1

Important Identified Risk:	Hypogammaglobulinemia
Risk groups or risk factors	Prior treatment with rituximab and concomitant use of other drugs (eg, steroids) that can induce hypogammaglobulinemia.
Preventability	Immunoglobulin levels should be monitored after treatment with Tecartus and managed using infection precautions, antibiotic prophylaxis and immunoglobulin replacement.
Impact on the benefit-risk balance of the product	Routine and additional pharmacovigilance activities will further characterize the risk of hypogammaglobulinemia with respect to number of reports, seriousness, outcome, and risk factors and determine if data is consistent with the information already known for this risk. The safe use of brexucabtagene autoleucel will be enhanced through routine risk minimization measures. The risk will be mitigated by these measures such that the benefit-risk for the product, considering the seriousness of the indication, is positive.
Public health impact	Minimal due to the relatively low number of people affected by the indication.

Abbreviations: CAR T = chimeric antigen receptor T cells

SVII.3.1.2. Important Potential Risks

Table SVII. 10. Important Potential Risk: Secondary Malignancy

Important Potential Risk:	Secondary Malignancy
Potential mechanisms	A possible mechanism is insertional mutagenesis of the viral vector or the development of RCR.
Evidence source and strength of evidence	No secondary malignancies were attributed to brexucabtagene autoleucel in clinical trials or post-marketing experience.
Characterization of the risk	**Clinical trials** **ZUMA-2 (as of 24 July 2021)** Overall, no secondary malignancies were attributed to brexucabtagene autoleucel in ZUMA-2. **ZUMA-3 (as of 23 July 2024)** No secondary malignancies were attributed to brexucabtagene autoleucel in ZUMA-3. **Post-marketing experience (cumulative to 23 January 2024)** There have been no new malignancy events that were attributable to brexucabtagene autoleucel.
Risk groups or risk factors	Patient factors: Age Additive or synergistic factors: Chemotherapy and immunosuppressive treatments
Preventability	HCPs should monitor patients' life-long for secondary malignancies. The SmPC includes recommendations for contacting the MAH to receive sampling advice. As part of site qualification training, HCPs are made aware of the need to contact the MAH to obtain recommendations for tumor sample collection and testing following the development of a secondary malignancy.

Important Potential Risk:	Secondary Malignancy
Impact on the benefit-risk balance of the product	Currently there is no substantive evidence of a causal relationship between brexucabtagene autoleucel and secondary malignancy. Hence, the risk-benefit balance for patients who already have a serious disease is not impacted. Routine pharmacovigilance activities will further characterize the risk of secondary malignancy with respect to number of reports, seriousness, outcome, and risk factors.
Public health impact	Minimal impact as causal relationship has not been established.

Abbreviations: HCP = healthcare professional; MAH = marketing authorization holder; RCR = replication-competent retrovirus; SmPC = summary of product characteristics.

Table SVII. 11. Important Potential Risk: Immunogenicity

Important Potential Risk:	Immunogenicity
Potential mechanisms	Mechanisms consist of humoral and cell-mediated immuno-reactivity which may include: an immunogenic reaction, including a T-cell-mediated immune response, against neo-epitopes associated with the brexucabtagene autoleucel CAR protein; an immune response to the murine scFv that can be present in the manufacturing process; and Type 1 hypersensitivity immune reactions {Lamers 2011, Song 2015}. The occurrence of immunogenicity is unlikely due to the initial presence or de novo formation of anti-brexucabtagene autoleucel antibodies due to the known on-target and off-tumor effects of brexucabtagene autoleucel, chemotherapy induced lymphodepletion and prior anti CD-20 therapy in most patients all of which reduce the number of normal B-cells.
Evidence source and strength of evidence	No brexucabtagene autoleucel related cases of immunogenicity were observed in ZUMA-2 in this cell based assay. In ZUMA-3, 2 subjects were confirmed to have antibodies to the anti-CD19 CAR after KTE-X19 infusion. One of these subjects was confirmed to be antibody-positive after retreatment with KTE-X19.
Characterization of the risk	**Clinical trials** **ZUMA-2 (as of 24 July 2021)** None reported. **ZUMA-3 (as of 23 July 2023)** As of 09 September 2020, in ZUMA-3, 15 subjects had positive antibody test results from initial screening assay: 9 subjects were antibody positive at baseline and 6 subjects who had negative test results at baseline had positive test results after Day 0. Available samples for 12 of the 15 subjects were further assessed with a confirmatory cell-based assay. Ten of the 12 subjects were confirmed to be antibody-negative at all time points tested, and 2 subjects were confirmed to be antibody-positive. One of the 2 subjects who were confirmed to be antibody-positive had a negative result at baseline and was confirmed to be antibody-positive at Month 6 after the brexucabtagene autoleucel infusion; the second subject had an unconfirmed positive antibody result at baseline and did not have sample available for confirmatory testing at this time point. The subject subsequently tested negative at Day 28 and Month 3 after the initial brexucabtagene autoleucel infusion. Following a relapse at Month 15, the subject was retreated with brexucabtagene autoleucel in accordance with the protocol specified retreatment criteria of no known neutralizing anti brexucabtagene autoleucel antibodies. This subject was confirmed to be antibody positive after retreatment with brexucabtagene autoleucel, at Retreatment Day 28 and Retreatment Month 3.

Important Potential Risk:	Immunogenicity
	Retrospective testing of a serum sample collected at Month 9 indicated an unconfirmed positive antibody result at this time point prior to retreatment, but no sample was available for confirmatory testing. As of 23 July 2023, there were no immunogenicity updates. **Post-marketing experience (cumulative to 24 January 2024)** Three events (3 cases) containing potential immunogenicity events were reported in the postmarketing setting. One case of fatal shock with an unknown cause of death, one case of anaphylactic shock, and one case of circulatory collapse, likely associated with clinical deterioration after a fall and subdural hematoma.
Risk groups or risk factors	None known.
Preventability	None
Impact on the benefit-risk balance of the product	From the current evidence, there is no impact on the risk-benefit of brexucabtagene autoleucel. Routine pharmacovigilance activities will further characterize the potential risk of immunogenicity with respect to number of reports, seriousness, outcome, and risk factors.
Public health impact	No impact based upon current evidence.

Abbreviations: CAR = chimeric antigen receptor; CD19 = cluster of differentiation 19; CD20 = cluster of differentiation 20; CRS = cytokine release syndrome; ELISA = enzyme linked immunosorbent assay; scFv = single chain variable region fragment.

Table SVII. 12. Important Potential Risk: RCR

Important Potential Risk:	RCR
Potential mechanisms	Retroviral vectors are engineered to be replication defective; however RCR may be generated during manufacturing through homologous or non-homologous recombination between the transfer vector, packaging components and endogenous retroviral elements in producer cells {Chong 1998, Garrett 2000}.
Evidence source and strength of evidence	There is no evidence for the occurrence of RCR in patients treated with Tecartus.
Characterization of the risk	**Clinical trials** **ZUMA-2 (as of 24 July 2021)** None reported. **ZUMA-3 (as of 23 July 2024)** None of the 97 subjects who had an evaluable sample for RCR testing at any time point were positive for RCR. There were no RCR updates in the 45-month follow-up per the protocol. **Post-marketing experience (cumulative to 24 January 2024)** None reported.
Risk groups or risk factors	Not applicable
Preventability	None

Important Potential Risk:	RCR
Impact on the benefit-risk balance of the product	No impact based upon current evidence. Routine and additional pharmacovigilance activities will further characterize the potential risk of RCR with respect to number of reports.
Public health impact	No impact based upon current evidence.

Abbreviations: RCR = replication-competent retrovirus

Table SVII. 13. Important Potential Risk: TLS

Important Potential Risk:	TLS
Potential mechanisms	TLS occurs when the cellular components of tumor cells are released into the blood after lysis.
Evidence source and strength of evidence	There have been low numbers of reports of TLS in clinical trials and none reported postmarketing.
Characterization of the risk	**Clinical trials** **ZUMA-2 Cohort 1 (as of 24 July 2021)** One subject in Cohort 1 had Grade 3 nonserious TLS, which was assessed as being related to brexucabtagene autoleucel. No additional cases of TLS were reported as of this 24-month analysis. **ZUMA-3 (as of 23 July 2023)** In ZUMA-3 Phase 1, 1 subject had Grade 3 serious tumor lysis syndrome, which was assessed as unrelated to brexucabtagene autoleucel. The event started on Day 29 and resolved on Day 34. In Phase 2, 1 subject had Grade 3 nonserious tumor lysis syndrome, which was assessed as related to brexucabtagene autoleucel. The event started on Day 9 and resolved on Day 36. The TLS occurred concurrently with Grade 1, 2, and 4 CRS, which started on Day 5 and resolved on Day 28. **Post-marketing experience (cumulative to 23 January 2024)** A total of 4 cases containing potential TLS events in the post-marketing setting. For all cases, a lack of information precludes an assessment of a potential causal association between brexucabtagene autoleucel and the reported event of TLS.
Risk groups or risk factors	Patient factors: Tumor size and presence of bulky tumor, wide metastatic dispersal, and organ and/or bone marrow involvement. Patients' health status, including presence of hypotension, dehydration, acidic urine, oliguria, pre-cancer nephropathy, and previous experience with nephrotoxic agents. Additive or synergistic factors: Medications and other compounds that tend to increase uric acid levels.
Preventability	Patients with elevated uric acid or high tumor burden should receive allopurinol, or an alternative prophylaxis, prior to Tecartus infusion. Signs and symptoms of TLS must be monitored, and events managed according to standard guidelines.
Impact on the benefit-risk balance of the product	Routine and additional pharmacovigilance activities will further characterize the potential risk of TLS with respect to number of reports, seriousness, outcome, and risk factors and that the data is consistent with the information already known for this potential risk. The safe use of brexucabtagene autoleucel will be enhanced through routine risk minimization measures. The potential risk will be mitigated by these measures such that the benefit-risk for the product, considering the seriousness of the indication, is positive.

Important Potential Risk:	TLS
Public health impact	Minimal due to the rarity of the condition.

Abbreviations: TLS = tumor lysis syndrome

Table SVII. 14. Important Potential Risk: Aggravation of GvHD

Important Potential Risk:	Aggravation of GvHD
Potential mechanisms	There is a theoretical risk of aggravation of GvHD in patients who have previously undergone an allo-HSCT and then received donor derived engineered CAR T cells (from prior allo-HSCT donor) for their relapsed MCL or ALL. The mechanism of aggravation of GvHD is via engraftment of immunocompetent donor T lymphocytes in an immunologically compromised host and having histocompatibility differences with the donor, resulting in donor T cell activation against either the recipient MHC antigens or minor histocompatibility antigens {Liu 2017}.
Evidence source and strength of evidence	There have been low numbers of reports of GvHD in clinical trials and none reported postmarketing.
Characterization of the risk	**Clinical trials** **ZUMA-2 (as of 24 July 2021)** None reported. **ZUMA-3 (as of 23 July 2023)** In ZUMA-3 Phase 1, 3 subjects had GvHD, none of which were assessed as related to brexucabtagene autoleucel. One subject had Grade 1 nonserious GvHD of the gastrointestinal tract on Day 176 following an allo-SCT on Day 94, which was ongoing as of the data cutoff date; 1 subject who had undergone allo-SCT prior to enrollment in ZUMA-3 experienced Grade 1 nonserious chronic GvHD of the skin and eyes that started on Day 51, which subsequently resolved on Day 489; 1 subject who had undergone allo-HSCT prior to enrollment in ZUMA-3 experienced worst Grade 2 serious GvHD of the gastrointestinal tract that started on Day 209 following a donor lymphocyte Infusion on Day 174, which subsequently resolved on Day 309. In Phase 2, 2 subject had GvHD. One participant had undergone allo-SCT prior to enrollment experienced worst Grade 2 GvHD, which was assessed as nonserious and related to brexucabtagene autoleucel. The other participant died on day 773 due to GvHD (worst grade 5), which was deemed unrelated to brexucabtagene autoleucel. **Post-marketing experience (cumulative to 23 January 2024)** None reported.
Risk groups or risk factors	Patients who had undergone a prior allo-HSCT and then received donor derived CAR T cells (from prior allo-HSCT donor) appear to be at an increased risk of developing aggravation of GvHD or GvHD.
Preventability	It is not recommended that patients who underwent an allo-HSCT and suffer from active acute or chronic GvHD receive treatment. Infusion must be delayed if a patient has active GvHD.
Impact on the benefit-risk balance of the product	From the current evidence, there is no impact on the risk-benefit of brexucabtagene autoleucel. Routine pharmacovigilance activities will further characterize the potential risk of GvHD or aggravation of GvHD with respect to number of reports, seriousness, outcome, and risk factors.

Important Potential Risk:	Aggravation of GvHD
Public health impact	No impact based upon current evidence.

Abbreviations: ALL = acute lymphoblastic leukemia; allo-HSCT = allogenic stem cell transplant; CAR T = chimeric antigen receptor T cells; GvHD = graft versus host disease; MCL = Mantle cell lymphoma; MHC = major histocompatibility complex.

SVII.3.2. Presentation of the Missing Information

Table SVII. 15. Missing Information

Missing Information:	Evidence source
New occurrence or exacerbation of an autoimmune disorder	Anticipated risk/consequence of the missing information: Production of brexucabtagene autoleucel involves modification of a patient's T cells, therefore there is a theoretical risk for exacerbating pre-existing autoimmune disorders or causing autoimmune disorders. Among the AEs associated with CRS is acute cytokine release and thus it is anticipated that patients with an autoimmune disorder will have a less favorable safety profile. It is conceivable that patients treated in a clinical setting may include those with autoimmune disorders. In the post-marketing setting, it is the responsibility of the prescribing physician to determine the appropriate treatment depending on the benefit-risk assessment of the treatment and condition. Risks of treating patients with an autoimmune disorder are not known and the benefit-risk assessment may be difficult to assess. The safety profile in this population will be derived from routine and additional pharmacovigilance activities.
Long term safety	Anticipated risk/consequence of the missing information: Specific safety events such as RCR and secondary malignancy may occur outside of the early post-administration period for brexucabtagene autoleucel. The planned additional pharmacovigilance registry for the long-term follow-up of patients post-treatment will collect this information.

Abbreviations: AE = adverse event; CRS = cytokine release syndrome; RCR = replication-deficient retrovirus.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII. 1. Summary of Safety Concerns

Important Identified Risks	Serious neurologic events, including cerebral edema
	CRS
	Cytopenias
	Infections
	Hypogammaglobulinemia
Important Potential Risks	Secondary malignancy
	Immunogenicity
	RCR
	TLS
	Aggravation of GvHD
Missing Information	New occurrence or exacerbation of an autoimmune disorder
	Long-term safety

Abbreviations: CRS = cytokine release syndrome; GvHD = graft versus host disease; RCR = replication competent retrovirus; TLS = tumor lysis syndrome.

PART III: PHARMACOVIGILANCE PLAN

III.1. Routine Pharmacovigilance Activities

The global safety database for brexucabtagene autoleucel is maintained and operated by Gilead Sciences, Inc. for reporting to regulatory authorities. All newly acquired safety information will continue to be actively monitored in accordance with good pharmacovigilance practices (GVP) including regular review and evaluation of data, routine systematic review of published literature and case reports, and both individual case and aggregate safety reviews and analysis.

Routine Pharmacovigilance Activities Beyond ADRs Reporting and Signal Detection:

Specific Adverse Reaction Follow-up Questionnaires

A copy of each follow-up questionnaire is provided in Annex 4.

Table Part III. 1. Specific Adverse Reaction Follow-up Questionnaires

Name of Questionnaire	Description
Neurologic events	The questionnaire is designed to obtain information related to neurologic events including start and stop dates of the event, severity and seriousness, outcome, diagnostic results, whether alternative causes for signs and symptoms were ruled out, treatment provided, relevant medical history, and additional medications.
Cytokine release syndrome	The questionnaire is designed to obtain information related to start and stop dates of the event, severity and seriousness, outcome, diagnostic results, whether alternative causes for signs and symptoms were ruled out, treatment provided, relevant medical history and additional medications. The questionnaire will also collect information on patients with underlying organ impairments (e.g., hepatic, renal, cardiac, pulmonary) who experience CRS.
New Malignancy	The questionnaire is designed to obtain information regarding start and stop dates of the event, severity and seriousness, diagnostic results, pre-existing factors that may have contributed to the development of the new malignancy, relevant medical history and additional medications.

Abbreviations: CRS = cytokine release syndrome.

Other Forms of Routine Pharmacovigilance Activities

There are no other forms of routine pharmacovigilance activities for any of the safety concerns.

III.2. Additional Pharmacovigilance activities

Table Part III. 2. Additional Pharmacovigilance Activities

KT-EU-472-5966: Tecartus Survey: Quantitative Testing of HCP Knowledge About Tecartus® Risk Minimization Measures	
Rationale and Study Objectives	The primary objective of the study is to measure the HCPs awareness and knowledge of RMMs for Tecartus, as described in the RMP; specifically, to conduct a survey to measure knowledge and understanding of the key messages in the HCP-directed additional RMMs and the SmPC for Tecartus, including how to mitigate the risks of CRS and neurological AEs. To meet this objective, the survey will: • Measure HCPs knowledge of known important identified risks associated with Tecartus. • Assess whether HCPs understand how to identify and treat CRS and serious neurologic AEs. • Assess whether HCPs are aware of the PAC, distribute the PAC, and inform patients about the PAC's content. • Assess HCP knowledge on the handling and administration
Study Design	Non-interventional, cross-sectional survey of HCPs
Study Populations	HCPs who have received training on the educational materials and prescribe or dispense Tecartus or manage patients experiencing Tecartus-related ADRs.
Milestones	Protocol submission: Protocol was submitted on 22 April 2021, amendment to the protocol (v2.0) was submitted on 22 February 2022. Final study report: Q4 2024

Abbreviations: ADR =adverse drug reaction; AE = adverse event; CRS = cytokine release syndrome; HCP = healthcare professional; PAC = patient alert card; RMM = risk minimization measures; SmPC = summary of product characteristics.

III.3. Summary Table of additional Pharmacovigilance activities

Table Part III. 3. Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
KT-EU-472-5966 Tecartus Survey: Quantitative Testing of HCP Knowledge About Tecartus® Risk Minimization Measures Planned	Assess the prescribers' understanding of the risks of brexucabtagene autoleucel. Evaluate the effectiveness of risk minimization activities: HCP educational materials, and Patient Alert Card.	Serious neurologic events including cerebral edema CRS	Protocol submission	Protocol v2.0 was submitted on 22 February 2022
			Final study report	Q4 2024

Abbreviations: CRS = cytokine release syndrome; HCP = healthcare professional; .

PART IV:
PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

The planned Tecartus Non-Interventional Registry Study will be conducted under one protocol as an efficacy and safety long-term follow up study. The objectives for both efficacy and safety will be evaluated based on a single data source (a registry) maintained by European Society for Bone and Marrow Transplantation (EBMT). In this study the objectives and milestones will be presented separately for efficacy and safety (see Table Part IV. 1 below).

Table Part IV. 1. Planned and Ongoing Post-authorization Efficacy Studies that are Conditions of the Marketing Authorization or that are Specific Obligations

Study Status	Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization				
KT-EU-472-6036 Long-term, non-interventional study of recipients of Tecartus for treatment of adult patients in all indications Planned	A prospective study to confirm the long-term efficacy and safety of Tecartus in adult patients with all indications and the Benefit/Risk in important subgroups: elderly, females, patients with severe disease	Overall response rate. Complete remission rate. Duration of response. Time to relapse or progression. Effectiveness by gender and age. Effectiveness in special populations.	Protocol submission	Protocol submitted on 08 March 2021
			Annual report	TBD
			Final study report	MCL: Q2 2042 ALL: Q4 2042
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
KT-EU-472-6036 Long-term, non-interventional study of recipients of Tecartus for treatment of adult patients with relapsed/refractory MCL Ongoing	A prospective study to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL and the Benefit/Risk in important subgroups: elderly, females, patients with severe disease	Efficacy in important subgroups	Protocol submission	Protocol submitted on 08 March 2021
			Annual report	TBD
			Final study report	MCL: Q2 2027

Study Status	Objectives	Efficacy uncertainties addressed	Milestones	Due Date
KTE-C19-103 (ZUMA-3) Phase 1/2, multicenter, open-label study evaluating the safety and efficacy of brexucabtagene autoleucel in adult subjects with relapsed/refractory B-ALL Ongoing	Primary objective of Phase 1: To evaluate the safety of brexucabtagene autoleucel. Primary objective of Phase 2: To evaluate the efficacy of brexucabtagene autoleucel, as measured by the overall complete remission rate defined as complete remission and complete remission with incomplete hematologic recovery in adult subjects with relapsed/refractory ALL. Secondary objectives: Assessing the safety and tolerability of brexucabtagene autoleucel, additional efficacy endpoints, and change in EQ-5D scores.		Specific obligation due date	31 March 2025*
			Final study report	September 2036
KTE-C19-102 (ZUMA-2) Completed	To confirm long term efficacy and safety in subjects treated with brexucabtagene autoleucel in Cohort 1	Long term efficacy	Final study report	Q1 2022
KT-EU-474-6644 Planned	Long-term efficacy and safety of Tecartus in adult patients with relapsed/refractory ALL.	Long term efficacy	Protocol submission	3 months following commission decision
			Final study report	31 December 2027

Abbreviations: ALL = acute lymphoblastic leukemia; MCL = Mantle cell lymphoma; TBD = to be determined.
*5-year follow-up interim results

PART V:
RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1. Routine risk minimization measures

The routine risk minimization measure for brexucabtagene autoleucel in the EU comprise of the summary of product characteristics (SmPC), the package leaflet (PL), and the legal status of the product. brexucabtagene autoleucel is subject to restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of hematological cancers (SmPC section 4.2). The routine risk minimization recommendations provided by the SmPC and PL are described further by safety concern in Table Part V. 1. The legal status can be considered a general measure applicable to all individual safety concerns.

Table Part V. 1. Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Serious neurologic events, including cerebral edema	**Routine risk communication**: SmPC sections: 4.2, 4.4, 4.7, 4.8 PL section: 2, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendations for monitoring and management of serious neurologic events, including treatment algorithms, are included in the SmPC sections 4.2, 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
CRS	**Routine risk communication**: SmPC sections: 4.2, 4.4, 4.8 PL section: 2, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendations for monitoring and management of CRS, including treatment algorithms, are included in the SmPC sections 4.2, 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
Cytopenias	**Routine risk communication**: SmPC sections: 4.4, 4.8 PL section: 2, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendation for blood count monitoring will be included in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.

Safety concern	Routine risk minimization activities
Infections	**Routine risk communication**: SmPC sections: 4.4, 4.8 PL section: 2, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendation for monitoring the signs and symptoms of infection before, during and after brexucabtagene autoleucel infusion and delay of infusion if a patient has an active uncontrolled infection are included in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
Hypogammaglobulinemia	**Routine risk communication**: SmPC sections: 4.4, 4.8 PL section: 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendations for monitoring immunoglobulin levels and management using infection precautions, antibiotic prophylaxis and immunoglobulin replacement are included in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
Secondary malignancy	**Routine risk communication**: SmPC section: 4.4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendation for life-long monitoring for secondary malignancies is included in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
Immunogenicity	**Routine risk communication**: SmPC section: 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
RCR	**Routine risk communication**: None **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.

Safety concern	Routine risk minimization activities
TLS	**Routine risk communication**: SmPC section: 4.4 PL section: 2 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendations that patients with elevated uric acid or high tumour burden receive treatment prior to infusion, and for monitoring and management of TLS are included in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
Aggravation of GvHD	**Routine risk communication**: SmPC section: 4.4 PL section: 2 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendation to delay of infusion if a patient has an active GvHD is included in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
New occurrence or exacerbation of an autoimmune disorder	**Routine risk communication**: None **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
Long term safety	**Routine risk communication**: None **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.

Abbreviations: CRS = cytokine release syndrome; GvHD = graft versus host disease; PL = package leaflet; RCR = replication competent retrovirus; SmPC = summary of product characteristics; TLS = tumor lysis syndrome.

V.2. Additional Risk minimization measures

Table Part V. 2. Additional Risk Minimization Activity: HCP Educational Material

HCP Educational Material	
Objective(s)	To inform HCPs on how to monitor and manage symptoms associated with CRS and serious neurologic adverse reactions and provide guidance on reporting these serious adverse reactions associated with brexucabtagene autoleucel.
Rationale for the additional risk minimization activity	The HCP educational material is provided as part of the treatment center qualification process. The HCP educational material will highlight the risks of brexucabtagene autoleucel and will help to ensure that the HCPs using brexucabtagene autoleucel are made aware of the risks and will be able to monitor for them. The HCP educational materials will also remind HCPs to ensure that they have access to a minimum of 1 dose of tocilizumab prior to brexucabtagene autoleucel infusion. The treatment center should have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, the treatment center must have access to suitable alternative measures instead of tocilizumab to treat CRS. CRS is not commonly observed with most anti-cancer medications. Therefore, HCPs may not be as experienced in managing these adverse reactions. It is anticipated that HCP educational material will enhance early diagnosis and proper evidence-based management of these events, including information on when and how to use tocilizumab and/or steroids. The expected result is improvement in the outcomes of or mitigating severe, life threatening, and fatal CRS and/or neurologic adverse reactions/ICANS.
Target audience and planned distribution path	The HCP educational material targets HCPs who prescribe or are likely to prescribe and use brexucabtagene autoleucel. The method of delivery of the HCP educational material is determined on a Member State basis to align with local treatment center organization.
Plans to evaluate the effectiveness of the interventions and criteria for success	Study KT-EU-472-5966, a prescriber survey, will evaluate HCP's knowledge of the risks associated with brexucabtagene autoleucel. An acceptable level of knowledge is set at 80%. Study KT-EU-472-6036, a long-term, non-interventional study will assess the incidence of serious neurologic adverse reactions and CRS and will thus provide an outcome measure of the effectiveness of the risk minimization program.
Rationale for proposing to remove additional risk minimization measure(s)	Not applicable.

Abbreviations: CRS = cytokine release syndrome; HCP = healthcare professional; ICANS = immune effector cell-associated neurotoxicity syndrome.

Table Part V. 3. Additional Risk Minimization Activity: PAC

PAC	
Objective(s)	To inform patients of the risks of CRS and serious neurologic adverse reactions/ICANS associated with brexucabtagene autoleucel. For patients to share the information in the PAC with their HCPs.
Rationale for the additional risk minimization activity	Easy and immediate patients' access to information about the common signs and symptoms of CRS and serious neurologic adverse reactions/ICANS will promote early medical attention and treatment that will help mitigate the risks.
Target audience and planned distribution path	The target audience is patients who will be treated with brexucabtagene autoleucel. The PAC will be part of the healthcare professional kit and will be provided to the patient by the hematologist/heme oncologist or nursing staff.
Plans to evaluate the effectiveness of the interventions and criteria for success	Study KT-EU-472-5966, a prescriber survey, will evaluate HCP's awareness and practices regarding the PAC.
Rationale for proposing to remove additional risk minimization measure(s)	Not applicable.

Abbreviations: CRS = cytokine release syndrome; HCP = healthcare professional; ICANS = immune effector cell-associated neurotoxicity syndrome; PAC = patient alert card.

Table Part V. 4. Additional Risk Minimization Activity: Controlled Distribution Program

Controlled Distribution Program	
Objective(s)	To ensure that brexucabtagene autoleucel is only administered in a qualified clinical setting.
Rationale for the additional risk minimization activity	To minimize the important risks of CRS and neurologic adverse reactions/ICANS, clinical facilities will be required to complete a formal site qualification process prior to ordering brexucabtagene autoleucel.
Target audience and planned distribution path	The controlled distribution program is intended to target clinical facilities in which brexucabtagene autoleucel will be administered. The process of qualification is carried out by the QA Site Qualification EU team at Kite Pharma EU BV. The site qualification process will include the following steps: • Introduction to key brexucabtagene autoleucel processes • Ensuring HCPs are made aware of the need to contact the MAH to obtain recommendations for tumor sample collection and testing following the development of a secondary malignancy of T cell origin • Quality Audit • Training of HCPs • "Dry-run exercise" • Continued monitoring of compliance

Controlled Distribution Program	
Plans to evaluate the effectiveness of the interventions and criteria for success	The evaluation of the effectiveness of the controlled distribution program will include a post-marketing registry which will assess the incidence of serious neurologic adverse reactions/ICANS and CRS and will thus provide an outcome measure of the effectiveness of the risk minimization program. This will assess whether the controlled distribution program is meeting its objectives.
Rationale for proposing to remove additional risk minimization measure(s)	Not applicable.

Abbreviations: CRS = cytokine release syndrome; EU = European Union; HCP = healthcare professional; ICANS = immune effector cell-associated neurotoxicity syndrome; QA = quality assurance.

V.3. Summary risk minimization measures

Table Part V. 5. Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
Serious neurologic events including cerebral edema	**Routine risk minimization measures**: SmPC sections: 4.2, 4.4, 4.7, 4.8 PL section: 2, 4 Recommendations for monitoring and management of serious neurologic events, including treatment algorithms, are included in the SmPC sections 4.2, 4.4. Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures**: ▪ HCP educational material ▪ PAC ▪ Controlled distribution program	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Event Follow-up Questionnaire **Additional pharmacovigilance activities**: KT-EU-472-5966: Q4 2024
CRS	**Routine risk minimization measures**: SmPC sections: 4.2, 4.4, 4.8 PL section: 2, 4 Recommendations for monitoring and management of CRS, including treatment algorithms, are included in the SmPC sections 4.2, 4.4. Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures**: ▪ HCP educational material ▪ PAC ▪ Controlled distribution program	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Event Follow-up Questionnaire **Additional pharmacovigilance activities**: KT-EU-472-5966: Q4 2024

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Cytopenias	**Routine risk minimization measures**: SmPC sections: 4.4, 4.8 PL section: 2, 4 Recommendation for blood count monitoring will be included in SmPC section 4.4. Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
Infections	**Routine risk minimization measures**: SmPC sections: 4.4, 4.8 PL section: 2, 4 Recommendation for monitoring the signs and symptoms of infection before, during and after brexucabtagene autoleucel infusion and delay of infusion if a patient has an active uncontrolled infection are included in SmPC section 4.4. Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
Hypogammaglobulinemia	**Routine risk minimization measures**: SmPC sections: 4.4, 4.8 PL section: 4 Recommendations for monitoring immunoglobulin levels and management using infection precautions, antibiotic prophylaxis and immunoglobulin replacement are included in SmPC section 4.4. Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
Important potential risk(s)		
Secondary malignancy	**Routine risk minimization measures**: SmPC section: 4.4 Recommendation for life-long monitoring for secondary malignancies is included in SmPC section 4.4. Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures**: ▪ Controlled distribution program	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Event Follow-up Questionnaire **Additional pharmacovigilance activities**: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Immunogenicity	**Routine risk minimization measures**: SmPC section: 4.8 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
RCR	**Routine risk minimization measures**: Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
TLS	**Routine risk minimization measures**: SmPC section: 4.4 PL section: 2 Recommendations that patients with elevated uric acid or high tumour burden receive treatment prior to infusion, and for monitoring and management of TLS are included in SmPC section 4.4. Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
Aggravation of GvHD	**Routine risk minimization measures**: SmPC section: 4.4 PL section: 2 Recommendation to delay of infusion if a patient has an active GvHD is included in SmPC section 4.4. Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing information		
New occurrence or exacerbation of an autoimmune disorder	**Routine risk minimization measures**: Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
Long-term safety	**Routine risk minimization measures**: Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None

Abbreviations: CRS = cytokine release syndrome; GvHD = graft versus host disease; HCP = healthcare professional; PAC = patient alert card; PL = package leaflet; RCR = replication competent retrovirus; SmPC = summary of product characteristics; TLS = tumor lysis syndrome.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

VI.1. SUMMARY OF RISK MANAGEMENT PLAN FOR TECARTUS (BREXUCABTAGENE AUTOLEUCEL)

This is a summary of the risk management plan (RMP) for Tecartus. The RMP details important risks of Tecartus, how these risks can be minimised, and how more information will be obtained about Tecartus's risks and uncertainties (missing information).

Tecartus's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Tecartus should be used.

This summary of the RMP for Tecartus should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Tecartus's RMP.

VI.2. The Medicine and What is it Used for

Tecartus is authorized for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor and for the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL) (see SmPC for the full indication). It contains brexucabtagene autoleucel as the active substance and it is given as a single infusion product for autologous and intravenous use only.

Further information about the evaluation of Tecartus's benefits can be found in Tecartus's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to the EPAR summary landing page:
https://www.ema.europa.eu/en/medicines/human/EPAR/tecartus

VI.3. Risks Associated with the Medicine and Activities to Minimise or Further Characterize the Risks

Important risks of Tecartus, together with measures to minimise such risks and the proposed studies for learning more about Tecartus's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the public (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Tecartus, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed (eg, via the periodic safety update report [PSUR]) so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Tecartus is not yet available, it is listed under 'missing information' below.

VI.3.A. List of important risks and missing information

Important risks of Tecartus are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tecartus. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table Part VI. 1. List of Important Risks and Missing Information

Important Identified Risks	Serious neurologic events, including cerebral oedema
	Cytokine release syndrome (CRS)
	Cytopenias
	Infections
	Hypogammaglobulinaemia
Important Potential Risks	Secondary malignancy
	Immunogenicity
	Replication competent retrovirus (RCR)
	Tumour lysis syndrome (TLS)
	Aggravation of graft versus host disease (GvHD)
Missing Information	New occurrence or exacerbation of an autoimmune disorder
	Long-term safety

VI.3.B. Summary of Important Risks

Tecartus has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby therapy must be administered in a qualified clinical setting, and be initiated by a doctor experienced in the management of haematological malignancies (as described in section 4.2 of the SmPC).

Table Part VI. 2. Summary of Important Risk(s) and Missing Information

Important Identified Risk	**Serious Neurologic Events including Cerebral Oedema**
Evidence for linking the risk to the medicine	Serious neurologic adverse events were reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.
Risk factors and risk groups	Female patients and subjects with higher ECOG performance status had a higher incidence of neurologic events.
Risk Minimization Measure(s)	**Routine risk minimisation measures**: SmPC sections: 4.2, 4.4, 4.7, 4.8 Package Leaflet (PL): 2, 4 Use restricted to physicians experienced in the treatment of haematological cancers. **Additional risk minimisation measures**: HCP educational material Patient Alert Card (PAC) Controlled distribution
Additional Pharmacovigilance activities	KT-EU-472-5966: Q4 2024 See section VI.3.C of this summary for an overview of the post-authorisation development plan.
Important Identified Risk	**Cytokine Release Syndrome**
Evidence for linking the risk to the medicine	CRS was reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.
Risk factors and risk groups	A higher disease burden, older age, organ dysfunction and female gender were associated with a higher rate of CRS.
Risk Minimization Measure(s)	**Routine risk minimisation measures**: SmPC sections: 4.2, 4.4, 4.8 PL section: 2, 4 Use restricted to physicians experienced in the treatment of haematological cancers. **Additional risk minimisation measures**: HCP educational material PAC Controlled distribution program
Additional Pharmacovigilance activities	KT-EU-472-5966: Q4 2024 See section VI.3.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk	**Cytopenias**
Evidence for linking the risk to the medicine	Cytopenias were reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.
Risk factors and risk groups	Prior exposure to chemotherapy or radiation.
Risk Minimization Measure(s)	**Routine risk minimisation measures**: SmPC sections: 4.4, 4.8 PL section: 2, 4 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimisation measures**: None
Additional Pharmacovigilance activities	None.
Important Identified Risk	**Infections**
Evidence for linking the risk to the medicine	Infections were reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.
Risk factors and risk groups	Patient factors: Underlying immune deficiencies, medical comorbidities, past infections, poor nutritional status, and psychological stress. Additive or synergistic factors: Surgery, radiation, immunosuppressant therapies, antimicrobial use, and invasive procedures.
Risk Minimization Measure(s)	**Routine risk minimisation measures**: SmPC sections: 4.4, 4.8 PL section: 2, 4 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimisation measures**: None
Additional Pharmacovigilance activities	None.
Important Identified Risk	**Hypogammaglobulinaemia**
Evidence for linking the risk to the medicine	Hypogammaglobinemia was reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.
Risk factors and risk groups	Prior treatment with rituximab and concomitant use of other drugs (eg, steroids) that can induce hypogammaglobulinaemia.
Risk Minimization Measure(s)	**Routine risk minimisation measures**: SmPC sections: 4.4, 4.8 PL section: 4 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimisation measures**: None
Additional Pharmacovigilance activities	None.

Important Potential Risk	**Secondary Malignancy**
Evidence for linking the risk to the medicine	No secondary malignancies were attributed to brexucabtagene autoleucel in clinical trials or post-marketing experience.
Risk factors and risk groups	Patient factors: Age Additive or synergistic factors: Chemotherapy and immunosuppressive treatments
Risk Minimization Measure(s)	**Routine risk minimisation measures**: SmPC section: 4.4 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimisation measures**: Controlled distribution program
Additional Pharmacovigilance activities	None.
Important Potential Risk	**Immunogenicity**
Evidence for linking the risk to the medicine	No brexucabtagene autoleucel related confirmed cases of immunogenicity were seen in ZUMA 2. In ZUMA-3, 2 subjects were confirmed to have antibodies to the anti CD19 CAR after brexucabtagene autoleucel infusion. One of these subjects was confirmed to be antibody-positive after retreatment with brexucabtagene autoleucel. Immunogenicity was reported in the post-marketing surveillance setting.
Risk factors and risk groups	None known.
Risk Minimization Measure(s)	**Routine risk minimization measures**: SmPC section: 4.8 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures**: None
Additional Pharmacovigilance activities	None.
Important Potential Risk	**RCR**
Evidence for linking the risk to the medicine	There is no evidence for the occurrence of RCR in patients treated with Tecartus.
Risk factors and risk groups	Not applicable
Risk Minimization Measure(s)	**Routine risk minimisation measures**: Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimisation measures**: None
Additional Pharmacovigilance activities	None.

Important Potential Risk	**TLS**
Evidence for linking the risk to the medicine	TLS was reported in clinical trials and post-marketing surveillance setting.
Risk factors and risk groups	Patient factors: Tumor size and presence of bulky tumor, wide metastatic dispersal, and organ and/or bone marrow involvement. Patients' health status, including presence of hypotension, dehydration, acidic urine, oliguria, pre-cancer nephropathy, and previous experience with nephrotoxic agents. Additive or synergistic factors: Medications and other compounds that tend to increase uric acid levels.
Risk Minimization Measure(s)	**Routine risk minimisation measures**: SmPC section: 4.4 PL section: 2 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimisation measures**: None
Additional Pharmacovigilance activities	None.
Important Potential Risk	**Aggravation of Graft versus Host Disease (GvHD)**
Evidence for linking the risk to the medicine	There have been low numbers of reports of GvHD in clinical trials and none reported postmarketing.
Risk factors and risk groups	Patients who had undergone a prior allo-HSCT and then received donor derived CAR T cells (from prior allo-HSCT donor) appear to be at an increased risk of developing aggravation of GvHD or GvHD.
Risk Minimization Measure(s)	**Routine risk communica**tion: SmPC section: 4.4 PL section: 2 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimisation measures**: None
Additional Pharmacovigilance activities	None.
Missing information	**New occurrence or exacerbation of an autoimmune disorder**
Risk Minimization Measures	**Routine risk minimisation measures**: Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimisation measures**: None
Additional Pharmacovigilance activities	None.
Missing information	**Long term safety**
Risk Minimization Measures	**Routine risk minimisation measures**: Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimisation measures**: None
Additional Pharmacovigilance activities	None.

VI.3.C. Post-authorization Development Plan

VI.3.C.1. Studies which are Conditions of the Marketing Authorization

Table Part VI. 3. Studies as Condition of the Marketing Authorization

Short Study Name	Purpose of the Study
KT-EU-472-6036	A prospective study to confirm the long-term efficacy and safety of Tecartus in adult patients with all indications and the Benefit/Risk in subgroups: elderly, females, patients with severe disease. Further evaluation of efficacy, additional characterisation of the identified risks, further evaluation of potential risks and missing information. This study will be designed as an efficacy and safety long-term follow up study.
ZUMA-3	Primary objective of Phase 1: To evaluate the safety of brexucabtagene autoleucel. Primary objective of Phase 2: To evaluate the efficacy of brexucabtagene autoleucel, as measured by the overall complete remission rate defined as complete remission and complete remission with incomplete hematologic recovery in adult subjects with relapsed/refractory ALL. Secondary objectives: Assessing the safety and tolerability of brexucabtagene autoleucel, additional efficacy endpoints, and change in EQ-5D scores.
KT-EU-474-6644	Long-term efficacy and safety of Tecartus in adult patients with relapsed/refractory ALL.

VI.3.C.2. Other Studies in Post-Authorization Development Plan

Table Part VI. 4. Other Studies in Post-Authorization Development Plan

Short Study Name	Purpose of the Study
KT-EU-472-5966	Evaluating the effectiveness of risk minimisation activities: HCP educational material and Patient Alert Card

PART VII: ANNEXES

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[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
Anna Vantroostenburg	QPPV eSigned	30-Sep-2024 07:12:11
[redacted]	Regulatory Affairs eSigned	30-Sep-2024 10:44:29
[redacted]	Patient Safety eSigned	30-Sep-2024 23:50:28

MCN: __ _____

EVENT FOLLOW-UP QUESTIONNAIRE - NEUROLOGIC EVENTS

Enter all dates in the following format: DD/MMM/YYYY

Patient			
Initials	Sex ☐ M ☐ F	DOB	Study ID (if applicable)
Product			
Name	Date dose	Indication	

Neurologic Adverse Event(s) – enter a diagnosis or signs/symptoms if a diagnosis is not available					
Neurologic Adverse Events(s)	**Start Date**	**Stop Date**	**CTCAE Grade[a]**	**Serious Criteria[b]**	**Outcome[c]**

Key:	CTCAE Grade[a]	Serious Criteria[b]	Outcome[c]
	1 = Grade 1 (mild) 2 = Grade 2 (moderate) 3 = Grade 3 (severe) 4 = Grade 4 (life-threatening) 5 = Fatal	D = Death L = Life-threatening H = Hospitalization/prolonged hospitalization S = Significant disability M = Medically significant N/A = Not applicable (non-serious)	1 = Recovered/resolved 2 = Recovering/resolving 3 = Not recovered/not resolved 4 = Recovered/resolved with sequelae 5 = Fatal 6 = Unknown

If one of the events resulted in death	Date of death:	Cause:
Was an autopsy performed?	☐ No ☐ Yes, request report	
Hospitalization	Admission date:	Discharge Date:

Diagnostic Results – enter N/A if not performed		
Diagnostic Test Date	**Brain Imaging or Other Diagnostic Results**	**Spinal Fluid Results**
Was any cerebral edema identified?	☐ Yes ☐ No	If yes, please describe how it was identified:

Additional Event Information		
In your opinion, what is the causal relationship between the neurologic adverse event and the Kite therapy? ☐ Related ☐ Not Related	If not related, what was the cause of the neurologic adverse event?	
Were alternate causes for the signs and symptoms ruled out?	☐ Yes ☐ No	If yes, please describe how these were ruled out:

Was tocilizumab administered? ☐ Yes ☐ No

Dose	Dates of Therapy	Response

Was an anti-epileptic administered? ☐ Yes ☐ No

Name of antiepileptic	Route	Dose	Therapy Dates	Response

Were corticosteroids (CS) administered? ☐ Yes ☐ No

Name of CS	Route	Dose	Therapy Dates	Response

Were any other treatments administered? ☐ Yes ☐ No

Name of treatment	Route	Dose	Therapy Dates	Response

Relevant Medical History (list below) or ☐ No medical history **If yes, please specify if any history of seizure disorder or other neurologic disorders, CNS involvement of cancer, previous treatment of CNS involvement of cancer or presence of implants or medical devices in the CNS.**	

Additional Medications (including concurrent medications) If list is too long, please include a printout of the patient's medications.				
Drug Name	**Indication**	**Dose and Frequency**	**Start Date**	**Stop Date**

Please provide any supplemental information on a separate page.

Signature of person completing form:	
Name of person completing form (Print):	Date Completed:
Email:	Phone:

MCN: __ _____

EVENT FOLLOW-UP QUESTIONNAIRE - CYTOKINE RELEASE SYNDROME (CRS)

Enter all dates in the following format: DD/MMM/YYYY

Patient			
Initials	Sex ☐ M ☐ F	DOB	Study ID (if applicable)
Product			
Name	Date dose	Indication	

CRS - Adverse Event (AE)			
Event	**Start Date**	**Stop Date**	**Outcome**
CRS			
CRS – associated AE (including Lab AEs) – list all below	**Start Date**	**Stop Date**	**Outcome**
CRS-associated organ specific AE (hepatic, renal, pulmonary or cardiac)- list all below			

Overall CRS Grade per Lee et al, Blood, 2014 – choose one		
☐	Grade 1	Symptoms are not life threatening and require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise)
☐	Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement <40% FiO_2 or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
☐	Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40% FiO_2 or Hypotension requiring high-dose or multiple vasopressors or

Overall CRS Grade per Lee et al, Blood, 2014 – choose one		
		Grade 3 organ toxicity or Grade 4 transaminitis

☐	Grade 4	Life-threatening symptoms Requirements for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
☐	Grade 5	Death

Serious Criteria (check all that apply):

☐ Death Date of death: ☐ Required or ☐ Prolonged hospitalization

Cause of death Admission Date Discharge Date

Was autopsy performed ☐ No ☐ Yes Request report ☐ Congenital anomaly/Birth defect

☐ Life-threatening ☐ Medically important

☐ Persistent or significant disability/incapacity ☐ Non-serious

In your opinion, what is the causal relationship between CRS and the Kite therapy? ☐ Related ☐ Not Related	If not related, what was the cause of the CRS?

Were alternate causes for he signs and symptoms ruled out? ☐ Yes ☐ No

If yes, describe how these were ruled out:

Was tocilizumab administered? ☐ Yes ☐ No

Dose	Dates of therapy	Response

Were corticosteroids (CS) administered? ☐ Yes ☐ No

Name of CS	Route	Dose	Therapy Dates	Response

Were anti-hypotension medications administered (pressors)? ☐ Yes ☐ No

Name of pressor	Dose	Therapy Dates	Response

Were any other treatments administered? ☐ Yes ☐ No

Name of treatment	Route	Dose	Therapy Dates	Response

Relevant Medical History (list below) or ☐ No medical history **If yes, please specify any infection history, including treatment for infection.** **If yes, please specify any history (including severity and previous treatment) of hepatic, renal, pulmonary or cardiac disease or impairment.**	

Additional Medications (including concurrent medications) If list is too long, please include a printout of the patient's medications.				
Drug Name	**Indication**	**Dose and Frequency**	**Start Date**	**Stop Date**

Please provide any supplemental information on a separate page.

Signature of person completing form:	
Name of person completing form (Print):	Date Completed:
Email:	Phone:

Please be aware that information provided to Gilead related to you may be used to comply with applicable laws and regulations. Gilead processes your personal or sensitive data in accordance with applicable data protection laws and the Gilead Privacy Statement. Available to you either on www.gilead.com/privacy or upon request.

MCN: __ _____

EVENT FOLLOW-UP QUESTIONNAIRE – New Malignancy

Enter all dates in the following format: DD/MMM/YYYY

Patient			
Initials	Sex ☐ M ☐ F	DOB	Study ID (if applicable)
Product			
Name	Date dose		Indication

New Malignancy- If not previously reported, please provide the information below

New Malignancy	Start Date	Stop Date	CTCAE Grade[a] (include CTCAE version)	Serious Criteria[b]	Outcome[c]

Key:	**CTCAE Grade[a]** 1 = Grade 1 (mild) 2 = Grade 2 (moderate) 3 = Grade 3 (severe) 4 = Grade 4 (life-threatening) 5 = Fatal	**Serious Criteria[b]** D = Death L = Life-threatening H = Hospitalization/prolonged hospitalization S = Significant disability M = Medically significant N/A = Not applicable (non-serious)	**Outcome[c]** 1 = Recovered/resolved 2 = Recovering/resolving 3 = Not recovered/not resolved 4 = Recovered/resolved with sequelae 5 = Fatal 6 = Unknown
If the event resulted in death	Date of death:	Cause:	Was autopsy performed? ☐ No ☐ Yes, provide report
If the event resulted in hospitalization		Admission date:	Discharge date:

Diagnostic Results – enter N/A if not performed		
Diagnostic Test Date	**Pathology: specify tissue type (including any additional analysis, molecular markers, etc.)**	**Imaging or Other Diagnostic Results**

Diagnostic Results – enter N/A if not performed		
Diagnostic Test Date	**Pathology: specify tissue type (including any additional analysis, molecular markers, etc.)**	**Imaging or Other Diagnostic Results**

Additional Event Information						
Pre-existing factors that may have contributed to the development of a new malignancy:						
In your opinion, what is the causal relationship between the new malignancy and the Kite therapy? ☐ Related ☐ Not Related		If not related, what was the cause of the new malignancy?				
If related, were alternate causes for the new malignancy ruled out?	Yes ☐ No ☐	If yes, please describe how these were ruled out:				
Were any treatments administered for the new malignancy?	☐ Yes ☐ No	Name of treatment:	Route:	Dose:	Therapy Dates:	Response:

Relevant Medical History ☐ Yes or ☐ No medical history or unknown **If yes, please describe below.**			
Cancer treatment received prior to Kite therapy	Please include below the dates of diagnosis and stage of disease, start and stop dates and specific agents of all cytotoxic chemotherapy/targeted therapy regimens as well as therapeutic radiation exposure.		
Diagnosis and stage:	Treatment regimen:	Dates of therapy:	Response:

Cancer treatment received after Kite therapy, but prior to new cancer diagnosis	Please include below the dates of diagnosis and stage of disease, start and stop dates and specific agents of all cytotoxic chemotherapy/targeted therapy regimens as well as therapeutic radiation exposure.		
Diagnosis and stage:	Treatment regimen:	Dates of therapy:	Response:
History of tobacco use? ☐Yes ☐ No		If yes, please provide the pack year history.	
History of environmental exposure (e.g., asbestos, radiation)? ☐Yes ☐ No		If yes, please describe.	
History of hereditary cancer syndromes? ☐Yes ☐ No		If yes, please describe.	
Family history of cancer ☐Yes ☐ No		If yes, please describe.	

Additional Medications (including concurrent medications) If list is too long, please include a printout of the patient's medications.				
Drug Name	**Indication**	**Dose and Frequency**	**Start Date**	**Stop Date**

Please provide any additional supplemental information on a separate page.

In the event that a new malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

Signature of person completing form: Click or tap here to enter text.	
Name of person completing form (Print):	Date Completed:
Email:	Phone:

Annex 6. Details of proposed additional risk minimization activities

Approved key messages of the additional risk minimization measures:

Site qualification and availability of tocilizumab

The Marketing Authorization Holder (MAH) will ensure that hospitals and their associated centers that dispense Tecartus are qualified in accordance with the agreed controlled distribution program by:

- ensuring immediate, on-site access to one dose of tocilizumab per patient prior to Tecartus infusion. The treatment center must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensuring that suitable alternative measures to treat cytokine release syndrome (CRS) instead of tocilizumab are available on-site.

- ensuring healthcare professionals (HCP) involved in the treatment of a patient have completed the educational program.

- As part of site qualification training, ensuring HCPs are made aware of the need to contact the MAH to obtain recommendations for tumor sample collection and testing following the development of a secondary malignancy of T cell origin.

HCP educational program

Prior to the launch of Tecartus in each Member State the MAH must agree the content and format of the HCP educational materials with the National Competent Authority.

The MAH shall ensure that in each Member State where Tecartus is marketed, all HCPs who are expected to prescribe, dispense, and administer Tecartus shall be provided with a guidance document to:

- facilitate identification of CRS and serious neurologic adverse reactions.

- facilitate management of the CRS and serious neurologic adverse reactions.

- ensure adequate monitoring of CRS and serious neurologic adverse reactions.

- facilitate provision of all relevant information to patients.

- ensure that adverse reactions are adequately and appropriately reported.

- before treating a patient, ensure that at least 1 dose of tocilizumab for each patient is available on site; in the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicine Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on site.

Patient educational program

A patient alert card to inform and explain to patients:

- the risks of CRS and serious neurologic adverse reactions, associated with Tecartus.
- the need to report the symptoms to their treating doctor immediately.
- the need to remain in the proximity of the location where Tecartus was received for at least 4 weeks following Tecartus infusion.
- the need to carry the patient alert card at all times.

Of note, the additional risk minimization measures for Tecartus are combined with Yescarta.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
[redacted]	Patient Safety eSigned	30-May-2024 23:16:20
Rainer Heissing	QPPV eSigned	31-May-2024 09:53:22
[redacted]	Regulatory Affairs eSigned	31-May-2024 15:42:23