EU Risk Management Plan for Tecartus

EU Risk Management Plan for Tecartus (brexucabtagene autoleucel)

RMP version to be assessed as part of this application:

Version number:	Data lock point for this RMP:	Date of final sign off:
4.0	**Clinical**: ZUMA-2: 24 July 2021 ZUMA-3: 09 September 2020 **Post-marketing**: 23 July 2021	Refer to Electronic Signatures

Abbreviations: RMP = risk management plan

Rationale for submitting an updated RMP: Update in response to information request.

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	Not applicable.
	Part II: Module SVIII - Summary of the Safety Concerns	Not applicable.

Part	Module/Annex	Significant Changes to RMP
Part III Pharmacovigilance Plan		Not applicable.
Part IV Plan for Post-authorization Efficacy Studies		Not applicable.
Part V Risk Minimization Measures		The following plan to evaluate effectiveness was reinstated: • Collection of evidence for the training delivered to HCPs and other relevant site personnel during site qualification. •
Part VI Summary of the Risk Management Plan		Not applicable.
Part VII Annexes	Annex 8	Updated to reflect changes made within the RMP.

Abbreviations: ALL = acute lymphoblastic leukemia; CRS = cytokine release syndrome; EU = European Union; HCP = healthcare professional; ICANS = immune effector cell-associated neurotoxicity syndrome; MCL = mantle cell lymphoma; RMP = risk management plan

Other RMP versions under evaluation

RMP Version number	Submitted on	Procedure number
3.3	04 April 2024	EMEA/H/C/005102/IB/0044

Abbreviations: RMP = risk management plan

Details of the currently approved RMP:

Version number	Approved with procedure	Date of approval
2.3 2.1	EMEA/H/C/005102/II/0008/G & EMEA/H/C/005102/II/0019	21 July 2022

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

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

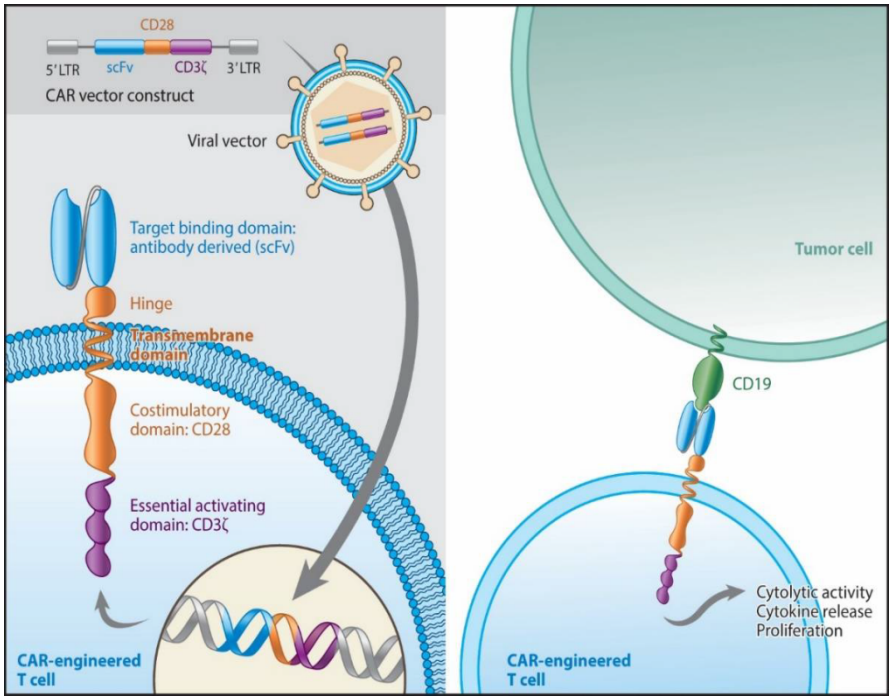
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

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
CRS	cytokine release syndrome
DoR	duration of remission
EPAR	European Public Assessment Report
EU	European Union
GvHD	graft versus host disease
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
PSUR	Periodic safety update report
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
TLS	tumor lysis syndrome
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

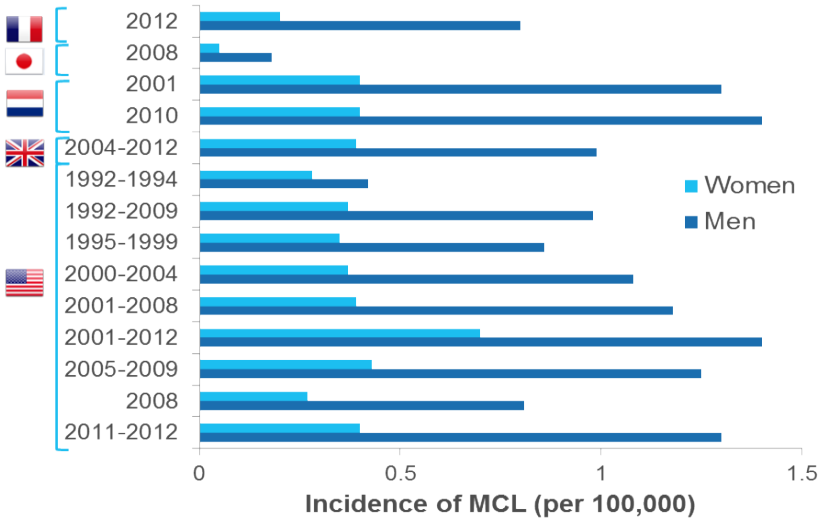
PART II: MODULE SI- EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

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}

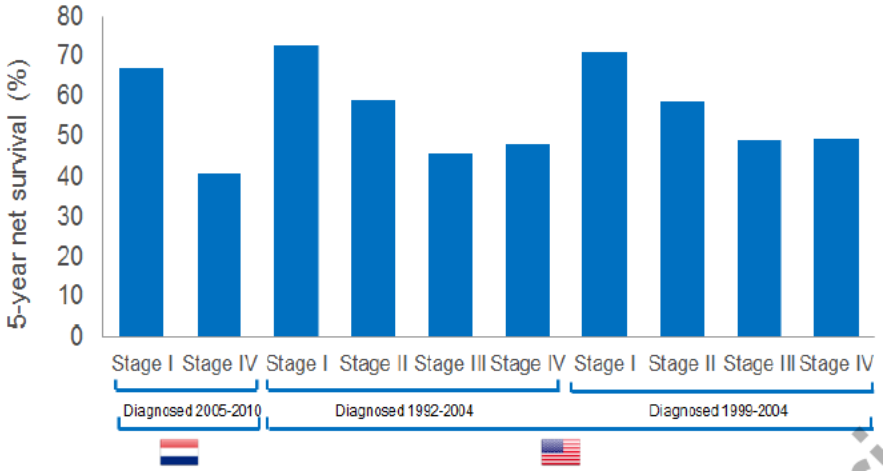
Abbreviation: MCL = mantle-cell lymphoma; mTOR = mammalian target of rapamycin; TNF-α = tumor necrosis factor-alpha

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

B-cell precursor acute lymphoblastic leukemia (B-ALL) is a malignant neoplasm of immature precursor B-cells that represents about 85% of all ALL cases {Nahar 2009}. The average age-standardized incidence rate of B-ALL in Europe has been reported as 1.2 per 100,000 population, with an average male to female incidence ratio of 1.2:1 ({Cancer Research UK 2021, HMRN 2019}). The highest incidence of B-ALL is reported in children ≤ 5 years and adults aged ≥ 50 years {Loghavi 2015}.

The most important biomarkers for B-ALL diagnosis are CD19, CD20, CD22, CD24, and CD79a {Chiaretti 2014}. Age and white blood count (WBC) are predictors of poor ALL prognosis and are used in risk stratification for ALL patients. Based on age and WBC, patients are classified for poor outcomes for ALL as follows: low risk (patients with no risk factors based on age and WBC); intermediate risk (patients aged >35 years or with elevated WBC [>30 x 10^9/L]) and high risk (patients aged >35 years and with elevated WBC [>30 x 10^9/L]). Survival prognosis based on this risk stratification is reported as 55% 5-year overall survival (OS) for low risk patients; 34% 5-year OS for intermediate risk patients, and 5% 5-year OS for high risk patients {Rowe 2005}.

SI.2.1. Incidence

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. Estimates from the CancerMpact registry on the incidence of ALL in 5 European countries (Germany, France, Spain, Italy and UK) in 2020 include an overall age-standardized incidence rate of 1.30 per 100,000 population. In the UK, during 2010-2016, the age-standardized incidence rate of B-ALL, was as 1.15 per 100,000 population {HMRN 2019}. The age-standardized incidence rate of ALL has remained stable over time in Europe as well as globally during 1990-2017 {Dong 2020}.

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}. This estimate is slightly higher than the age-standardized incidence rate of B-ALL reported in the HMRN registry between 2010-2016 (0.90 per 100,000 population). The HAEMACARE study, a European commission funded cancer registry-based project covering approximately 30% of the European population reported a crude IR (95% CI) of 0.08 (0.07-0.10) per 100,000 for B-ALL from 2000-2002 {Sant 2010}. This crude incidence of B-ALL reported in the HAEMACARE is, however, much lower than expected using the proportion of 85% reported by Nahar {Nahar 2009}, which might be due to a difference in ALL classification (revised in 2001 {Vardiman 2002}).

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)			

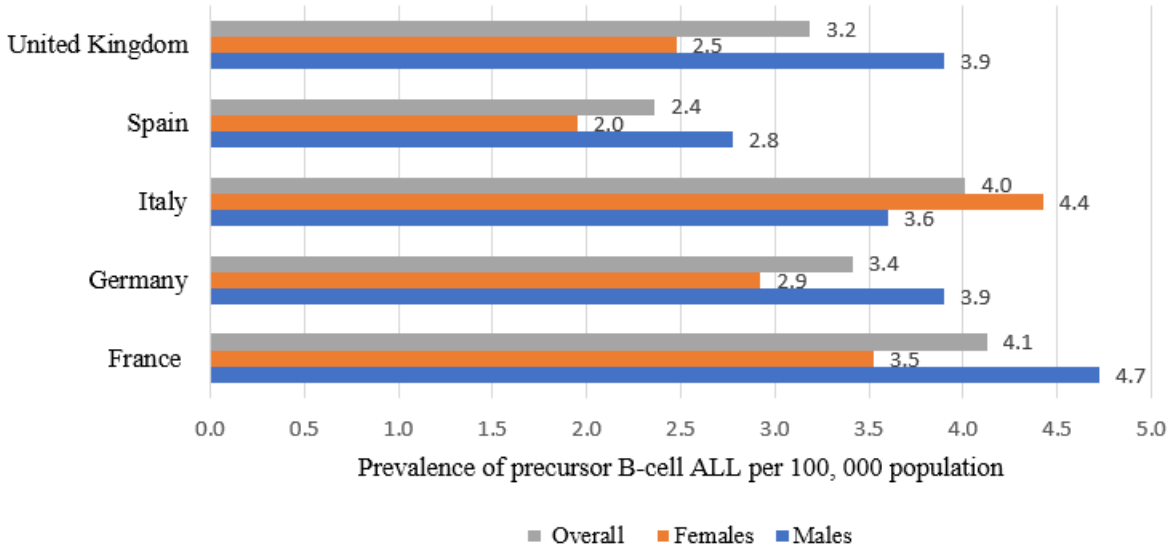
Source	Country	Period/Year	Crude Incidence Rate/100,000 population (95% CI)	Age-standardized Incidence Rate/ 100,000 population	Age-standardized Incidence Rate by sex/100,000 population	
					Male	Female
B-ALL						
{CancerMPact 2020}	Europe	2020	-	1.11[b]	1.19[b]	1.02[b]
{HMRN 2019}	United Kingdom	2010-2016	-	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}.

According to CancerMpact, the overall male to female ratio for the 5-year prevalence estimates of ALL for the 5 European countries in 2020 shown in Figure SI.3 was 1.2: 1 (5.0 versus 4.1). In all countries except for Italy, males had a higher prevalence of ALL and B-ALL in comparison to females.

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. Chemotherapy treatment for ALL typically involves the following distinct phases: induction, intensified consolidation, and maintenance. 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.

Second-line Therapies

For patients with relapsed/refractory Ph+ disease, treatment may include TKIs in combination with any induction regimens that were not previously given, although treatment resistance is common among those receiving TKI-containing regimens in the first line, and patients should be

considered for allo-SCT, if possible {National Comprehensive Cancer Network (NCCN) 2021, Ottmann 2009}. Although disease-free survival rates with allo-SCT are superior to those with chemotherapy in the salvage setting, only 30% to 40% of patients who achieve a second CR are eligible for allo-SCT, and fewer than half are able to undergo transplant before experiencing relapse {Fullmer 2009}.

The bispecific CD19-directed CD3 T-cell engaging agent blinatumomab has been approved in the US and EU for the treatment of relapsed/refractory B-ALL. Blinatumomab has also been approved for MRD+ B-ALL in the frontline setting (first or second CR). The TOWER study was a Phase 3, randomized, open-label, active-comparator study of 405 subjects with Ph–, relapsed/refractory B-ALL (refractory to primary induction therapy or to last therapy, untreated first relapse with a first remission duration of < 12 months, untreated second or later relapse, or relapse at any time after allo-SCT) {Blincyto 2020, Kantarjian 2017}. In total, 271 subjects were randomly assigned to receive blinatumomab, and 134 subjects were randomly assigned to receive standard-of-care chemotherapy. The primary endpoint, OS, was significantly longer in the blinatumomab arm compared with the chemotherapy arm (median OS of 7.7 months vs 4.0 months, respectively; p = 0.012). Blinatumomab treatment also resulted in superior remission rates compared with chemotherapy, as measured by the secondary endpoints of CR rate (33.6% vs 15.7%, respectively) and the combined rate of CR/CR with incomplete hematologic recovery (CRi) (35.1% vs 20.1%, respectively) {Kantarjian 2017}. Among all subjects with CR/CRi/complete remission with partial hematologic recovery, the median duration of remission (DoR) was 7.3 months in the blinatumomab arm and 4.6 months in the chemotherapy arm.

In 2017, inotuzumab ozogamicin (hereafter referred to as inotuzumab), a CD22-directed antibody-drug conjugate, was approved in the US and EU for the treatment of adults with relapsed/refractory B-ALL. Approval was based on findings from the Phase 3, randomized, open-label, multicenter INO-VATE study of 326 subjects with $CD22^{+}$, relapsed/refractory B-ALL {European Medicines Agency 2017}. Subjects were randomly assigned 1:1 to receive either inotuzumab or the investigator's choice of chemotherapy. The primary endpoints of the study were CR/CRi rate and OS {Kantarjian 2016}. The primary efficacy analysis was based on the first 218 subjects who underwent randomization. The CR/CRi rate was significantly higher for subjects in the inotuzumab arm compared with the chemotherapy arm (80.7% vs 29.4%, respectively; p < 0.001), with CR rates of 35.8% and 17.4%, respectively (p = 0.002). The MRD rate among subjects who achieved a CR/CRi was higher for the inotuzumab arm compared with the chemotherapy arm (78.4% vs 28.1%, respectively; p < 0.001). In a follow-up analysis including all 326 subjects who underwent randomization, the CR/CRi rate among treated subjects was 73.8% in the inotuzumab arm and 35.0% in the chemotherapy arm, and the median DoR among subjects who achieved a CR/CRi was 5.4 months in the inotuzumab arm and 4.2 months in the chemotherapy arm {Kantarjian 2019}.

The study failed to meet its coprimary endpoint of improvement in OS with inotuzumab as compared with chemotherapy (median OS of 7.7 months vs 6.7 months, respectively; p = 0.04), based on a prespecified threshold for significance of p = 0.0208 {Kantarjian 2016}. Ultimately, approval for inotuzumab was granted based on the CR, DoR, and MRD– rates observed with this treatment {BESPONSA 2020}.

Third-line Therapies

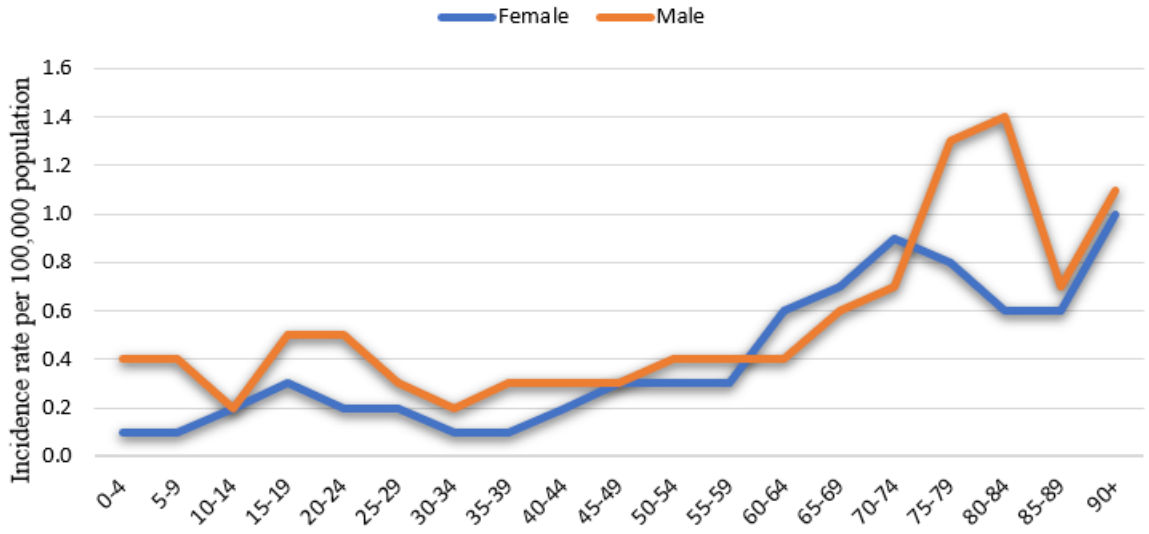
Patients in their second or later relapse may receive therapies typically utilized in the second line, such as allo- or autologous stem cell transplantation. However, few patients in this setting are eligible for SCT. Therapies approved for the second line, such as blinatumomab or inotuzumab, may also be utilized in the third line if not previously used, although outcomes with these treatments are typically not as favorable in patients being treated in the third line and beyond. Subjects receiving blinatumomab as a third or later line of therapy for B-ALL had a median OS of 5.1 months compared with 11.1 months for those receiving blinatumomab as their second line {Dombret 2019}. In the INO-VATE study, the CR/CRi rate was 77.8% for subjects receiving inotuzumab as the second line and 66.1% for those receiving inotuzumab as the third line {Kantarjian 2019}. Because of these poor outcomes with third-line and higher therapies, the National Comprehensive Cancer Network and European Society for Medical Oncology recommend that patients seeking treatment for relapsed/refractory B-ALL participate in clinical trials {Hoelzer 2016, National Comprehensive Cancer Network (NCCN) 2021}. This further highlights the need for novel therapies, especially ones that can be effective for disease that is refractory or in second or later relapse.

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}. In a large MRC trial to investigate optimal therapy for adults with ALL, patients aged ≥60 years were found to have the lowest long term survival rate (10-15%) {Rowe 2005}. 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. In this trial, the 5-year OS rates were as follows: 55% for patients classified as low risk (no risk factors according to age and WBC risk stratification); 34% for patients classified as intermediate risk (age >35 years or elevated WBC) and 5% for high risk patients (age >35 years and elevated 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 July 2021, approximately 272 participants have been administered brexucabtagene autoleucel in the clinical trial program.

Table SIII.1. Cumulative Subject Exposure to brexucabtagene autoleucel from Ongoing Clinical Trials by Age and Sex (as of 23 July 2021)

Age (Years)	Male (N=183)	Female (N=89)	Total (N=272)
< 18	27	19	46
18 to 65	113	51	164
> 65	43	19	62
Total	183	89	272

Source: PSUR#2
Note: Data from ongoing studies as of 23 July 2021.
Data Source: ADSL Program Name: t_ex_age_sex Output Generated: 20210819T09:48

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

Racial group	Number of subjects (N=272)
White	216
Other	34
Asian	8
Black or African American	6
Missing	5
Native Hawaiian or Other Pacific Islander	2
American Indian or Alaska native	1
Total	272

Source: PSUR#2
Note: Data from ongoing studies as of 23 July 2021.
Abbreviations: N = Number of subjects treated with KTE-X19
Compassionate use subjects are not included.
Data Source: ADSL Program Name: t_ex_race Output Generated: 20210819T09:48

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 and Phase 2, Safety Analysis Set; N=100)

	Phase 1 and Phase 2 (N = 100)
Actual follow-up time from KTE-X19 dose (months) [a]	
n	100
Mean (Std Dev)	13.9 (11.3)
Median (Q1, Q3)	12.2 (3.8, 17.9)
Min, Max	0.2, 51.7
Potential follow-up time from KTE-X19 dose (months) [b]	
n	100
Mean (Std Dev)	26.2 (12.2)
Median (Q1, Q3)	21.3 (16.0, 38.7)
Min, Max	10.3, 53.5
Subjects with ≥ 1 month potential follow-up [b], n (%)	100 (100)
Subjects with ≥ 3 months potential follow-up [b], n (%)	100 (100)
Subjects with ≥ 6 months potential follow-up [b], n (%)	100 (100)
Subjects with ≥ 9 months potential follow-up [b], n (%)	100 (100)
Subjects with ≥ 12 months potential follow-up [b], n (%)	96 (96)
Subjects with ≥ 15 months potential follow-up [b], n (%)	81 (81)
Subjects with ≥ 18 months potential follow-up [b], n (%)	67 (67)
Subjects with ≥ 24 months potential follow-up [b], n (%)	45 (45)
Subjects with ≥ 30 months potential follow-up [b], n (%)	35 (35)
Subjects with ≥ 36 months potential follow-up [b], n (%)	29 (29)
Subjects with ≥ 42 months potential follow-up [b], n (%)	11 (11)
Subjects with ≥ 48 months potential follow-up [b], n (%)	6 (6)

Data cutoff date = 09Sep2020.
Abbreviations: Q1 = first quartile; Q3 = third quartile; Std Dev = 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, ADEX Program Name: t_ds Output Generated: 20210406T08:12
Source: Table14.1.2.3

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 09 Sep 2020, 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 09 Sep 2020 was 12.2 (3.8, 17.9) months.	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	Post-exposure observation time in clinical trials is limited to up to 56 months as of 24 July 2021.	There is no evidence of new signals in subjects who were followed for up to 56 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 July 2021 is estimated to be 344. 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

	Estimated Patient Exposure
Geographic Area	**Cumulatively**
USA	286
EEA[a] and UK	58
Total[b]	**344**

Abbreviations: EEA = European Economic Area; UK = United Kingdom; 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, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden

b A total of 127 KTE-X19 lots have been shipped in the compassionate use setting cumulatively in the USA, Canada, UK Switzerland and EEA countries and are not included in the above 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%).

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). Among the 68 subjects who experienced neurologic events, the median time to onset was 7 days (range: 1 to 31 days) after brexucabtagene autoleucel infusion. Neurologic events reported in ≥5% of subjects are presented below.

Neurologic Events Occurring in ≥5% of Subjects 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 neurologic event	68 (68)	13 (13)	23 (23)	27 (27)	4 (4)	1 (1)
Confusional state	29 (29)	10 (10)	13 (13)	5 (5)	1 (1)	0 (0)
Encephalopathy	29 (29)	4 (4)	10 (10)	11 (11)	4 (4)	0 (0)
Tremor	28 (28)	24 (24)	3 (3)	1 (1)	0 (0)	0 (0)
Aphasia	22 (22)	3 (3)	6 (6)	13 (13)	0 (0)	0 (0)
Agitation	13 (13)	4 (4)	6 (6)	3 (3)	0 (0)	0 (0)
Seizure	8 (8)	2 (2)	2 (2)	4 (4)	0 (0)	0 (0)
Delirium	6 (6)	2 (2)	2 (2)	2 (2)	0 (0)	0 (0)
Somnolence	6 (6)	3 (3)	1 (1)	2 (2)	0 (0)	0 (0)
Lethargy	5 (5)	2 (2)	3 (3)	0 (0)	0 (0)	0 (0)
Mental status changes	5 (5)	0 (0)	4 (4)	1 (1)	0 (0)	0 (0)

Data cutoff date = 09Sep2020.
Abbreviations: AE = adverse event; 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 23.0 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 et al 2015).
Data Source: ADSL, ADAE Program Name: t_ne Output Generated: 20201211T10:12
Source: Table 14.3.17.1.3

Important Identified Risk:	Serious Neurologic Events including Cerebral Edema

Serious neurologic events reported in ZUMA-3 are summarized below. Encephalopathy, aphasia, confusional state and seizure occurred in ≥5% of subjects, the remaining events occurred in ≤2% of subjects. There was one Grade 5 event of brain herniation.

Subject Incidence of Serious 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 = 09Sep2020.
Abbreviations: AE = adverse event; 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 23.0 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 et al 2015).
Data Source: ADSL, ADAE Program Name: t_ne Output Generated: 20201211T10:12
Source: Table 14.3.17.2.3

Reversibility

Neurologic events resolved for 61 out of 68 subjects with a median duration of 10 days (range: 1 to 236 days). Six subjects had ongoing neurologic events at the time of death, including 1 subject with the reported events of serious encephalopathy, cerebral edema and cerebral herniation, 2 subjects with serious encephalopathy, 1 subject with serious paralysis and an additional subject with serious paraparesis. The remaining unresolved neurologic events were Grade 1, Grade 2, or nonserious.

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

Important Identified Risk:	Serious Neurologic Events including Cerebral Edema

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 July 2021)

Serious Neurologic Events including Cerebral Edema reported in the Post-marketing Setting (Cumulative to 23 July 2021)

Category		Value
Total number of Cases		43
Total number of Events		83
	Serious	68
	Non-Serious	15
Event Outcomes		
	Fatal	4
	Lost to follow-up	0
	Not Reported	23
	Not Resolved	11
	Resolved	30
	Resolved with Sequelae	0
	Resolving	9
	Unknown	6
Time to event onset range (median) days		0-31 (7)
Events by PT (descending order)		
	Immune effector cell-associated neurotoxicity syndrome	24
	Neurotoxicity	16
	Encephalopathy	7
	Confusional state	3
	Disorientation	3
	Memory impairment	3
	Tremor	3
	Agitation	2
	Aphasia	2
	Brain oedema	2
	Delirium	2
	Dysgraphia	2
	Seizure	2
	Somnolence	2
	Cognitive disorder	1
	Coma	1
	Depressed level of consciousness	1
	Epilepsy	1
	Lethargy	1
	Mental status changes	1
	Paraesthesia	1
	Speech disorder	1

Important Identified Risk:	Serious Neurologic Events including Cerebral Edema
	Status epilepticus: 1 Unresponsive to stimuli: 1 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. Patients must be monitored daily for the first 7 days following infusion for signs and symptoms of potential neurologic events. Physicians can consider hospitalization for the first 7 days or at the first signs or 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 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 to 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 summarized 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). 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. The incidence of CRS observed in ≥5% of subjects in ZUMA-3 is presented below.

Important Identified Risk:	Cytokine Release Syndrome

The median time to onset was 4 days (range 1 to 12 days). No subject in ZUMA-3 had new onset CRS that started >13 days after the cell infusion.

Subject Incidence of CRS in ≥5% of Subjects 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 [a]	91 (91)	19 (19)	47 (47)	15 (15)	9 (9)	1 (1)
CRS symptoms by preferred term [b] (N = 91)						
Pyrexia	82 (90)	9 (10)	37 (41)	32 (35)	4 (4)	0 (0)
Hypotension	62 (68)	3 (3)	29 (32)	24 (26)	6 (7)	0 (0)
Sinus tachycardia	31 (34)	11 (12)	16 (18)	4 (4)	0 (0)	0 (0)
Chills	27 (30)	21 (23)	6 (7)	0 (0)	0 (0)	0 (0)
Hypoxia	25 (27)	1 (1)	5 (5)	12 (13)	7 (8)	0 (0)
Tachycardia	24 (26)	9 (10)	13 (14)	2 (2)	0 (0)	0 (0)
Headache	18 (20)	9 (10)	8 (9)	1 (1)	0 (0)	0 (0)
Fatigue	14 (15)	9 (10)	5 (5)	0 (0)	0 (0)	0 (0)
Nausea	11 (12)	4 (4)	7 (8)	0 (0)	0 (0)	0 (0)
Malaise	6 (7)	6 (7)	0 (0)	0 (0)	0 (0)	0 (0)
Tachypnoea	5 (5)	2 (2)	2 (2)	0 (0)	1 (1)	0 (0)

Data cutoff date = 09Sep2020.
Abbreviations: AE = adverse event; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events.
Note: Preferred terms are sorted in descending order of total frequency in the 'Any' column.
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.

a. CRS is graded per the revised grading system proposed by Lee et al (2014). The percentages are calculated using the total number of subjects in the safety analysis set as the denominator.
b. Individual CRS symptoms are graded per CTCAE 4.03. Percentages are calculated using the number of subjects with any treatment-emergent CRS of any grade.

Data Source: ADSL, ADAE Program Name: t_crs Output Generated: 20201211T10:11
Source: Table 14.3.16.1.3

As of the data cut-off date (09 Sept 2020), CRS had resolved in 86 of the 91 subjects who experienced CRS events. The median duration of CRS symptoms was 4 days (range: 1 to 12 days).

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 July 2021)
<table>
<tr><td colspan="3">CRS Events reported in the Post-marketing Setting (Cumulative to 23 July 2021)</td></tr>
<tr><td>Category</td><td></td><td>Value</td></tr>
<tr><td>Total number of Cases</td><td></td><td>41</td></tr>
<tr><td>Total number of Events</td><td></td><td>42</td></tr>
<tr><td></td><td>Serious</td><td>42</td></tr>
<tr><td></td><td>Non-Serious</td><td>0</td></tr>
<tr><td>Events Grade 3 or higher</td><td></td><td>5</td></tr>
<tr><td>Event Outcomes</td><td></td><td></td></tr>
<tr><td></td><td>Fatal</td><td>0</td></tr>
<tr><td></td><td>Lost to follow-up</td><td>0</td></tr>
<tr><td></td><td>Not Reported</td><td>18</td></tr>
<tr><td></td><td>Not Resolved</td><td>5</td></tr>
<tr><td></td><td>Resolved</td><td>13</td></tr>
<tr><td></td><td>Resolved with Sequelae</td><td>0</td></tr>
<tr><td></td><td>Resolving</td><td>2</td></tr>
<tr><td></td><td>Unknown</td><td>4</td></tr>
<tr><td>Time to event onset range (median) days</td><td></td><td>0-9 (5)</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. Patients must be monitored daily for the first 7 days following infusion for signs and symptoms of potential CRS. Physicians can consider hospitalization for the first 7 days or at the first signs or 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 of a qualified treatment centre for at least 4 weeks following infusion and 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.

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 = 09Sep2020.
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 23.0 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: 20201211T10:12
Source: Table 14.3.19.1.3.

Reversibility

In ZUMA-3, subject incidence of Grade ≥3 cytopenias present on or after Day 30 included neutropenia 28%, anemia 12%, and thrombocytopenia 17%.

Post-marketing experience (cumulative to 23 July 2021)

Cytopenia Events reported in the Postmarketing Setting (Cumulative to 23 July 2021)

Category		Value
Total number of Cases		5
Total number of Events		6
	Serious	5
	Non-Serious	1
Event Outcomes		
	Fatal	0
	Lost to follow-up	0
	Not Reported	0
	Not Resolved	1

Important Identified Risk:	Cytopenias		
		Resolved	5
		Resolved with Sequelae	0
		Resolving	0
		Unknown	0
	Time to event onset range (median) days		2-7 (5)
	Events by PT (descending order)		
		Febrile neutropenia	2
		Pancytopenia	2
		Cytopenia	1
		Neutropenia	1
	Abbreviations: PT = preferred term.		
Risk groups or risk factors	Prior exposure to chemotherapy or radiation.		
Preventability	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.		
Impact on the benefit-risk balance of the product	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.		
Public health impact	Minimal due to the relatively low number of people affected by the indication.		

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

Important Identified Risk:	Infections
	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%). In ZUMA-3, under the SOC of infections and infestations, 44 subjects (44%) had AEs of any grade. Events of infections reported in ≥5% of subjects were sepsis (9 subjects, 9%), bacteremia (7 subjects, 7%), pneumonia (7 subjects, 7%), upper respiratory infection (5 subjects, 5%). Fourteen subjects (14%) had Grade 3 events, 8 subjects (8%) had Grade 4 events and 8 subjects (8%) had a Grade 5 event. Infections by type are presented below: **Bacterial infections**: Twelve (12%) of subjects had bacterial infections, including 6% with Grade 3 or higher bacterial infections. The most common bacterial infection preferred terms of any grade were clostridium difficile infection, enterococcal bacteremia, and escherichia bacteremia (2% each). All other bacterial infections occurred in 1 subject each (1%). Four subjects (4%) had a Grade 3 bacterial infections (enterococcal bacteraemia, escherichia bacteraemia, cellulitis, cellulitis of male external genital organ, pseudomonas infection, wound infection staphylococcal). Two subjects (2%) had Grade 4 infections (enterococcal bacteraemia, escherichia sepsis). No subject had a Grade 5 bacterial infection. **Viral infections**: Five (5%) of subjects had any grade viral infection; including 2% with Grade 2, 2% with Grade 3 and 1% with Grade 5. All viral infections occurred in 1 subject (1%) each. One subject had a Grade 5 event of herpes simplex viremia. Opportunistic infections: 5% of subjects had an opportunistic infection; 1% with Grade 2 (cytomegalovirus viraemia), 3% with Grade 3 (osteomyelitis fungal, pneumocystis jirovecii pneumonia, sinusitis fungal) and 1% with Grade 5 (fungal pneumonia). **Other infections**: Thirty-one (31%) of subjects had “other” infections, 11% were Grade 3, 7% were Grade 4 and 6% were Grade 5. The most common other infections of any grade were sepsis (9%), bacteraemia (7%), pneumonia (7%), upper

<table>
<tr><th>Important Identified Risk:</th><th>Infections</th></tr>
<tr><td></td><td>respiratory tract infection (5%), urinary tract infection (3%), and septic shock (2%). Eleven subjects (11%) had a Grade 3 other infection: pneumonia, 4 subjects; bacteraemia and upper respiratory tract infection, 3 subjects each; urinary tract infection, 2 subjects. The remaining Grade 3 other infections occurred in 1 subject each. Seven subjects (7%) had a Grade 4 other infection including sepsis in 5 subjects. The remaining Grade 4 other infections occurred in 1 subject each. Six subjects (6%) had a Grade 5 other infection: sepsis, 3 subjects; bacteraemia, pneumonia, and septic shock, 1 subject each.
Post-marketing experience (cumulative to 23 July 2021)
<table>
<tr><th colspan="3">Infection Events reported in the Postmarketing Setting (Cumulative to 23 July 2021)</th></tr>
<tr><th>Category</th><th></th><th>Value</th></tr>
<tr><td>Total number of Cases</td><td></td><td>2</td></tr>
<tr><td>Total number of Events</td><td></td><td>5</td></tr>
<tr><td></td><td>Serious</td><td>5</td></tr>
<tr><td></td><td>Non-Serious</td><td>0</td></tr>
<tr><td>Event Outcomes</td><td></td><td></td></tr>
<tr><td></td><td>Fatal</td><td>0</td></tr>
<tr><td></td><td>Lost to follow-up</td><td>0</td></tr>
<tr><td></td><td>Not Reported</td><td>5</td></tr>
<tr><td></td><td>Not Resolved</td><td>0</td></tr>
<tr><td></td><td>Resolved</td><td>0</td></tr>
<tr><td></td><td>Resolved with Sequelae</td><td>0</td></tr>
<tr><td></td><td>Resolving</td><td>0</td></tr>
<tr><td></td><td>Unknown</td><td>0</td></tr>
<tr><td>Events by PT (descending order)</td><td></td><td></td></tr>
<tr><td></td><td>Cytomegalovirus viraemia</td><td>1</td></tr>
<tr><td></td><td>Endocarditis</td><td>1</td></tr>
<tr><td></td><td>Infection</td><td>1</td></tr>
<tr><td></td><td>Peritonitis bacterial</td><td>1</td></tr>
<tr><td></td><td>Sepsis</td><td>1</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 09 September 2020)** In ZUMA-3, 7 subjects (7%) experienced hypogammaglobulinemia. Five of the 7 subjects received intravenous immunoglobulin therapy. **Post-marketing experience (cumulative to 23 July 2021)** None reported.
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	The increased incidence of other malignant neoplasms is attributed to disease- and/or therapy related immunosuppression and/or genotoxicity, including the administration of conditioning therapy prior to the administration of brexucabtagene autoleucel {Tsimberidou 2009}. Another possible mechanism is insertional mutagenesis of the viral vector, or RCR, which may be created by a recombination between endogenous retroviral element and the viral vector, will integrate into genomic regions that will interfere with the transcription of certain genes and this genotoxicity will result in secondary malignancy.
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 09 September 2020)** In ZUMA-3, 2 subjects with potential secondary malignancies were identified, both events were assessed as unrelated to brexucabtagene autoleucel. One of the 2 subjects had an AE of MDS related to prior therapy and 1 had an AE of leukemic retinopathy that was likely due to underlying disease. **Post-marketing experience (cumulative to 23 July 2021)** None reported.
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.
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 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. 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. **Post-marketing experience (cumulative to 23 July 2021)** None reported.
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 09 September 2020)** In ZUMA-3, at the time of data cutoff, none of the 97 subjects who had an evaluable sample for RCR testing at any time point were positive for RCR. **Post-marketing experience (cumulative to 23 July 2021)** None reported.
Risk groups or risk factors	Not applicable
Preventability	None
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 09 September 2020)** 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

Important Potential Risk:	TLS
	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 July 2021)** None reported.
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.
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 09 September 2020)** 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

Important Potential Risk:	Aggravation of GvHD
	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, 1 subject who had undergone allo-SCT prior to enrollment experienced worst Grade 2 GvHD, which was assessed as nonserious and related to brexucabtagene autoleucel. **Post-marketing experience (cumulative to 23 July 2021)** 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.
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.

Missing Information:	Evidence source
	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: Q2 2024
KTE-C19-108 (ZUMA-8): Phase 1 multicenter, open-label study evaluating the safety and tolerability of brexucabtagene autoleucel in adult subjects with relapsed/refractory CLL and SLL	
Rationale and Study Objectives	Primary objective: Evaluate the safety and tolerability of brexucabtagene autoleucel in subjects with relapsed or refractory CLL and SLL. Secondary objectives: To characterize the safety profile and anti- brexucabtagene autoleucel antibodies, and to evaluate the efficacy of brexucabtagene autoleucel as measured by the objective response rate per investigator review in subjects with relapsed/refractory CLL treated with brexucabtagene autoleucel. Efficacy analysis for objective response rate will be performed only for the selected safe dose cohort. Exploratory Objectives: Exploratory objectives are to characterize the safety profile and endpoints including complete response/complete response with incomplete hematopoietic recovery rate, minimal residual disease negativity rate, complete response/minimal residual disease rate, duration of response, progression-free survival, overall survival, and to evaluate biomarkers, pharmacokinetic analysis, and pharmacodynamic markers of CAR T-cell function, immune activation, and alloimmunization. Available nodal biopsies will be used to investigate levels of B-cell markers (e.g., CD19, CD20) and attributes of the tumor microenvironment (eg, levels of T-cell infiltration). Efficacy analysis endpoints listed will only be explored for the selected safe dose cohort.
Study Design	A Phase 1, multicenter, open-label study
Study Populations	Adult subjects with relapsed/refractory CLL and SLL
Milestones	Safety updates in the nearest PSUR to the annual anniversary: Annual

Abbreviations: ADR =adverse drug reaction; AE = adverse event; CAR T = chimeric antigen receptor T cells; CD19 = cluster of differentiation 19; CD20 = cluster of differentiation 20; CLL = chronic lymphocytic leukemia; HCP = healthcare professional; PAC = patient alert card; PSUR = periodic safety update report; RMM = risk minimization measures; RMP = risk management plan; SLL = small lymphocytic lymphoma; 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	Q2 2024
KTE-C19-108 (ZUMA-8) Phase 1 multicenter, open-label study evaluating the safety and tolerability of brexucabtagene autoleucel in adult subjects with relapsed/refractory CLL and SLL Ongoing	To evaluate the safety and tolerability of brexucabtagene autoleucel in adult subjects with relapsed/refractory CLL and SLL	Serious neurologic events including cerebral edema CRS Cytopenias Infections Hypogammaglobulinemia Secondary malignancy Immunogenicity RCR TLS Aggravation of GvHD New occurrence or exacerbation of an autoimmune disorder Long term safety	Safety updates in the nearest PSUR to the annual anniversary	Annual
			Final study report	December 2036

Abbreviations: ALL = acute lymphoblastic leukemia; B-ALL = B-cell precursor acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia; CRS = cytokine release syndrome; GvHD = graft versus host disease; HCP = healthcare professional; MCL = Mantle cell lymphoma; PSUR = periodic safety update report; RCR = replication-competent retrovirus; SLL = small lymphocytic lymphoma; TBD = to be determined; TLS = tumor lysis syndrome.

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 Ongoing	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: Q1 2043 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 October 2024*
			Final study report	September 2036
KT-EU-474-6644 Long-Term, Non-Interventional Study of the Treatment by Tecartus of Adult Patients with Relapsed or Refractory B-cell ALL Planned	Long-term efficacy and safety of Tecartus in adult patients with relapsed/refractory ALL.	Long term efficacy	Protocol submission	16 December 2022
			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 the following: • Collection of evidence for the training delivered to HCPs and other relevant site personnel during site qualification. • 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. These activities 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: Q2 2024 ZUMA-8: Dec 2036
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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Event Follow-up Questionnaire **Additional pharmacovigilance activities**: KT-EU-472-5966: Q2 2024 ZUMA-8: Dec 2036

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Additional risk minimization measures: ▪ HCP educational material ▪ PAC ▪ Controlled distribution program	
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**: ZUMA-8: Dec 2036
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**: ZUMA-8: Dec 2036
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**: ZUMA-8: Dec 2036
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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Event Follow-up Questionnaire

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures**: ▪ Controlled distribution program	**Additional pharmacovigilance activities**: ZUMA-8: Dec 2036
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**: ZUMA-8: Dec 2036
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**: ZUMA-8: Dec 2036
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**: ZUMA-8: Dec 2036
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**: ZUMA-8: Dec 2036

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**: ZUMA-8: Dec 2036
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**: ZUMA-8: Dec 2036

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

I. 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.

II. 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

III. 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.

III.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

III.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: Q2 2024 ZUMA-8: Dec 2036 See section III.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: Q2 2024 ZUMA-8: Dec 2036 See section III.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	ZUMA-8: Dec 2036 See section III.C of this summary for an overview of the post-authorisation development plan.
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	ZUMA-8: Dec 2036 See section III.C of this summary for an overview of the post-authorisation development plan.
Important Identified Risk	**Hypogammaglobulinaemia**
Evidence for linking the risk to the medicine	Hypogammaglobinemia was reported in clinical trials 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	ZUMA-8: Dec 2036 See section III.C of this summary for an overview of the post-authorisation development plan.

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	ZUMA-8: Dec 2036 See section III.C of this summary for an overview of the post-authorisation development plan.
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.
Risk factors and risk groups	None known.
Risk Minimization Measure(s)	**Routine risk minimisation measures**: SmPC section: 4.8 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimisation measures**: None
Additional Pharmacovigilance activities	ZUMA-8: Dec 2036 See section III.C of this summary for an overview of the post-authorisation development plan.
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	ZUMA-8: Dec 2036 See section III.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk	**TLS**
Evidence for linking the risk to the medicine	There have been low numbers of reports of TLS in clinical trials and none reported postmarketing.
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	ZUMA-8: Dec 2036 See section III.C of this summary for an overview of the post-authorisation development plan.
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	ZUMA-8: Dec 2036 See section III.C of this summary for an overview of the post-authorisation development plan.
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	ZUMA-8: Dec 2036 See section III.C of this summary for an overview of the post-authorisation development plan.

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	ZUMA-8: Dec 2036 See section III.C of this summary for an overview of the post-authorisation development plan.

III.C. Post-authorization Development Plan

III.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.

III.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
KTE-C19-108 (ZUMA-8)	To evaluate the safety and tolerability of brexucabtagene autoleucel in adult subjects with relapsed/refractory CLL and SLL

PART VII: ANNEXES

Table of Contents

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[redacted]	Regulatory Affairs eSigned	11-Apr-2024 12:23:22

Tabulation Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Table 1. Planned and Ongoing Studies

Study	Summary of Objectives	Safety Concern addressed	Milestones
Planned studies			
KT-EU-472-5966 Tecartus Survey: Quantitative Testing of HCP Knowledge About Tecartus® Risk Minimization Measures Category 3	Assess the prescribers' understanding of the risks of KTE-X19. Evaluate the effectiveness of risk minimization activities: HCP educational materials, and Patient Alert Card	Serious neurologic events including cerebral edema CRS	Protocol v2.0 was submitted on 22 February 2022 Final study report: Q2 2024
Ongoing studies			
KTE-C19-108 (ZUMA-8) Phase 1, multicenter, open-label study evaluating the safety and tolerability of KTE-X19 in adult subjects with relapsed/refractory CLL and SLL Category 3	To evaluate the safety and tolerability of KTE-X19 in adult subjects with relapsed/refractory CLL and SLL	Serious neurologic events including cerebral edema CRS Cytopenias Infections Hypogammaglobulinemia Secondary malignancy Immunogenicity RCR TLS Aggravation of GvHD New occurrence or exacerbation of an autoimmune disorder Long term safety	Safety updates in the nearest PSUR to the annual anniversary Final study report: December 2036

Abbreviations: ALL = acute lymphoblastic leukemia; B-ALL = B-cell precursor acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia; CRS = cytokine release syndrome; GvHD = graft versus host disease; HCP = healthcare professional; MCL = Mantle cell lymphoma; PSUR = periodic safety update report; RCR = replication-competent retrovirus; SLL = small lymphocytic lymphoma; TBD = to be determined; TLS = tumor lysis syndrome.

Table 2. Completed Studies

Study	Summary of Objectives	Safety Concern Addressed	Date of Final Study Report Submission Link to Report
None	Not applicable	Not applicable	Not applicable

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Annex 3. Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

Study Number and Title	Protocol Version and Date	Procedure number
Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP		
None		
Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP		
None		
Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority.		
***Approved protocols**:*		
None		
***Final protocols not reviewed or not approved**:*		
KT-EU-472-5966 EMA/CHMP/PRAC/338792/2021	v2.0 22 February 2022	22 February 2022
KTE-C19-108 (ZUMA-8)	Amendment 3 01 September 2021	Not applicable

The following studies included in the pharmacovigilance plan are planned and protocols are not currently available: None

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NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDY PROTOCOL

Study Title:	Tecartus Survey: Quantitative Testing of Health Care Professional Knowledge About Tecartus® Risk Minimisation Measures
Protocol ID:	KT-EU-472-5966
Protocol Version/Date:	2.0, 16 February 2022
EU PAS Register Number:	TBD
Clinical Trials.gov Identifier:	N/A
Active Substance:	Autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3ζ chimeric antigen receptor and cultured
Medicinal Product:	Tecartus
Product Reference:	EMEA/H/C/005102
Procedure Number:	TBD
Joint Post-authorisation Safety Study:	No
Research Question and Objective:	The primary objective of the study is to measure the health care professionals' awareness and knowledge of the risk minimisation measures (RMMs), addressing the key important identified risks associated with the use of Tecartus and their understanding of the handling and administration of Tecartus. The target population are HCPs from qualified centres in Europe who prescribe, dispense, handle, or administer Tecartus, or manage patients experiencing Tecartus related adverse events (AEs) and received training on the additional RMMs.
Countries of Study:	In countries where Tecartus is expected to be launched, including the Czech Republic, France, Germany, Great Britain Italy, the Netherlands, Poland, Portugal and Spain.
Gilead Study Director/ Author/Contact Person:	Heribert Ramroth, PhD Phone: +44 (0) 20 8587 2560

Marketing Authorisation Holder:	Kite Pharma EU B.V. Tufsteen 1 2132 NT Hoofddorp The Netherlands
Gilead Qualified Person Responsible for Pharmacovigilance:	Anne-Ruth van Troostenburg de Bruyn, GP, MD (London), FFPM, DipPharmMedRCP Phone: +49 (0) 89 8998 90181

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse events
CAR	chimeric antigen receptor
CRO	clinical research organization
CRS	cytokine release syndrome
EMA	European Medicines Agency
EU	European Union
GLPS	Gilead Global Patient Safety
GVP	Good Pharmacovigilance Practices
HCP	health care professional
PAC	patient alert card
RMM	risk minimisation measures
RMP	Risk Management Plan
US	United States

1. RESPONSIBLE PARTIES

Table 1-1. Responsible Parties

Responsibility	Name, Title, Qualifications, Affiliation, and Address	Contact Information
Marketing Authorisation Holder	Kite Pharma EU B.V. Tufsteen 1 2132 NT Hoofddorp The Netherlands	Phone: +44 1223 824642 Email: Anne-Lise.Stanley@gilead.com
Study Director	Heribert Ramroth, Sr Director, Real-World Evidence 2 Roundwood Avenue Stockley Park Uxbridge UB11 1AF, UK	Phone: +44 (0) 20 8587 2560 Email: Heribert.Ramroth@gilead.com
Medical Monitor	Daniel Lee, Sr Director, Safety & Pharmacovigilance Kite Pharma, a Gilead Company 2400 Broadway Santa Monica, CA 90404 USA	Phone: +1 424 416 8909 Email: Dlee07@kitepharma.com
Clinical Operations	Antonio Llamas, Associate Director, Clinical Operations Gilead Sciences, S.L. Parque Empresarial Cristalia Edificio 7/8, planta 6a C/ Vía de los Poblados, 3. 28033 Madrid, Spain	Phone: +34 91 114 2210 Email: Antonio.Llamas@gilead.com
Global Patient Safety	Global Patient Safety (GLPS) Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA	Phone: +1 800 445 3235 Fax: +1 650 522 5477 Email: Safety_fc@gilead.com
European Union Qualified Person for Pharmacovigilance	Anne-Ruth van Troostenburg de Bruyn, Vice President, GLPS Gilead Sciences GmbH Fraunhoferstr. 17 82152 Martinsried Germany	Phone: +49 (0) 89 899 890 181 Email: Anna.vanTroostenburg@gilead.com

2. PROTOCOL SYNOPSIS/ABSTRACT

Kite Pharma Inc
2400 Broadway
Santa Monica, CA 90404
United States of America

Title:	Tecartus Survey: Quantitative Testing of Health Care Professional Knowledge About Tecartus® Risk Minimisation Measures
Rationale and Background:	Tecartus was authorised in Europe on 14 December 2020 for the treatment of adult patients with relapsed/refractory mantle cell lymphoma after ≥ 2 lines of systemic therapy, including a Bruton's tyrosine kinase inhibitor. To ensure safe and effective use, Tecartus was authorised with additional risk minimisation measures (RMMs) in Europe. These additional RMMs include educational material targeted for both health care professional (HCPs) and patients (via the patient alert card [PAC]). The primary aim is to inform HCPs and patients about important risks associated with Tecartus, including cytokine release syndrome (CRS) and serious neurologic adverse events (AEs), as well as the correct handling and administration of Tecartus. Use of Tecartus is restricted to physicians experienced in the treatment of haematological cancers who have been trained on the RMMs during the site qualification process or annual retraining, if applicable. Another key risk mitigation measure is to ensure hospitals or clinics treating patients with Tecartus have immediate access on-site to tocilizumab to manage the risk of CRS. The rationale of conducting the survey is to measure the effectiveness of the additional RMMs for Tecartus, as described in the Risk Management Plan (RMP), version 1.0, dated 09 October 2020. The survey will assess HCPs knowledge of the risks of Tecartus and its risk minimisation strategies as outlined in the routine and additional RMMs.
Research Question and Objective:	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 Summary of Product Characteristics (SmPC) for Tecartus, including how to mitigate the risks of CRS and neurological AEs and how to correctly handle and administer Tecartus to ensure product viability.

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 the relevant HCPs understand the correct way of handling and method of administration of Tecartus to maintain product viability
- Assess whether HCPs are aware of the PAC, distribute the PAC, and inform patients about the PAC's content.

Study Design:

The study is a non-interventional, cross-sectional survey of HCPs based in Europe. The survey will be conducted ≥ 12 months after Tecartus has been introduced in Europe. The survey will be distributed to HCPs who have received training on additional RMMs and prescribe, dispense, handle, or administer Tecartus or manage patients experiencing Tecartus-related adverse events (AEs), which will ensure these selected HCPs have been trained on the educational materials ≥ 6 months prior to completing the survey as part of the site qualification process or annual retraining, if applicable.

The survey will be conducted in countries where Tecartus has been launched, including the Czech Republic, France, Germany, Great Britain, Italy, the Netherlands, Poland, Portugal, and Spain

The survey will undergo cognitive pretesting in up to 10 HCPs who prescribe, handle, dispense, or administer Tecartus or manage patients who experience Tecartus-related AEs. Pretesting will be performed to identify any survey questions that require clarification or revision based on areas of confusion or miscomprehension to avoid potentially negative study results based on misunderstood or poorly worded questions.

Based on the results of the qualitative testing, the questions for the survey may be revised accordingly.

Population:

Inclusion Criteria

1) Is an HCP who has received training on the educational materials and prescribes, handles, dispenses, or administers Tecartus, or manages patients experiencing Tecartus-related AEs.

Exclusion Criteria

1) Is an HCP who has participated in qualitative pretesting of the Tecartus survey

2) Is an HCP who has confirmed that they or any of their immediate family members have ever directly worked for Kite Pharma, Inc., Gilead Sciences, Inc., ICON, or the European Medicines Agency (EMA).

Variables: Responder demographic variables will include medical specialty, practice setting, and country. These will also include the capacity in which the HCP works and whether they are handling and administering Tecartus, and/or managing patient care and Tecartus-related AEs.

This study will not collect patient level data.

Data Sources: The data source for the survey will be HCPs who received training on the additional RMMs during the site qualification process or annual retraining, if applicable.

The survey will be open for 6 months and the minimum number of completed surveys is expected to reach 100. If 100 completed surveys are not received within 6 months of launch, contingency plans will be implemented, which may include inviting additional HCPs who were trained after 30 September 2021 (the training cutoff date for the survey), and outreach via a different modality.

Study Size: Details are provided in Section 7.5.

Data Analysis: Responses to questions for all completed surveys will be analysed using descriptive statistics (count, ranges, proportions, and scores). HCPs knowledge will be evaluated and expressed as proportions or scores. The results will be presented overall, as well as by country and HCP specialty where sample size allows. Categorical variables will be described by the number and proportion in each category. Frequency point-estimates with 2-sided 95% confidence intervals using the binomial distribution (eg, Wald or Clopper-Pearson method, as appropriate) will be constructed to describe the proportion of HCPs aware of the specified risks.

Key questions within the survey were identified as being essential to measure HCPs knowledge of the additional RMMs. Given the complexity of some of the key messages included in the Tecartus RMMs, an acceptable level of knowledge on these essential questions is set at 80%.

Milestones:	Start of data collection: The survey will be conducted ≥ 12 months after Tecartus has been introduced in Europe. The survey will be distributed in quarter 4 2022 to all HCPs who have received training on additional RMMs and prescribe, handle, dispense, or administer Tecartus or manage patients experiencing Tecartus-related AEs, which will ensure selected HCPs have been trained on the educational materials ≥ 6 months prior to completing the survey as part of the site qualification process or annual retraining, if applicable. End of data collection: The survey will be open for 6 months. Final study report: within 12 months of the end of data collection, anticipated to be at the end of the third quarter of 2023.

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices and Heads of Medicines Agencies Good Pharmacovigilance Practices, including archiving of essential documents.

3. AMENDMENTS AND UPDATES

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason for Update
1.1	20 August 2021	• Section 4. • Section 7.1 Study Design • Section 7.4 Data Sources • Section 7.7 Data analysis • Section 7.9: Limitation of Research Methods	• 1.1	• Milestones: Milestone have been updated. • Updated to indicate 1 additional country will be included. • Updated to include PRAC feedback. • Updated to include relevant key survey questions and incorporating PRAC feedback. • Updated to include the limited sample size and variability between the countries • Rephrased some of the content as a follow up to PRAC feedback
2.0	11 February 2022	• Section 2 • Section 5.1 Rationale for the current study • Section 6 Research question and objective • Section 7 — Section 7.1 Survey Design — Section 7.2 Setting — Section 7.3 Variables — Section 7.5 Study Size — Section 7.7 Data analysis	• 2.0	• Updated to include objectives to assess handling and administration of Tecartus

Abbreviation: NA, not applicable; PRAC, Pharmacovigilance Risk Assessment Committee.

Protocol Modifications

Protocol modifications may be made only by Kite Pharma, Inc. (hereafter referred to as Kite), a wholly owned subsidiary of Gilead Sciences, Inc. (hereafter referred to as Gilead). Any planned amendments will be discussed with the regulatory authority.

4. MILESTONES

Table 4-1. Protocol Milestones

Milestone	Planned Date
Protocol submission	Q1 2022
Registration in the EU PAS register	Q2/Q3 2022
Survey launch	Q4 2022
Survey closure	Q2 2023
Final report of study results	Q3 2023

Abbreviation: Q, quarter.

5. RATIONALE AND BACKGROUND

5.1. Rationale for the Current Study

Tecartus® (autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3ζ chimeric antigen receptor [CAR] and cultured) is a gene therapy medicinal product containing autologous T cells genetically modified ex vivo using a retroviral vector encoding an anti-CD19 CAR comprising a murine anti-CD19 single-chain variable region fragment linked to the CD28 costimulatory domain and CD3ζ signalling domain. It was launched in Europe on 14 December 2020 for the treatment of adult patients with relapsed/refractory mantle cell lymphoma after ≥ 2 lines of systemic therapy, including a Bruton's tyrosine kinase inhibitor. To ensure safe and effective use, Tecartus was authorised with additional risk minimisation measures (RMMs) in the Europe. These additional RMMs include educational material targeted for both health care professionals (HCPs) and patients (via the patient alert card [PAC]). The primary aim is to inform HCPs and patients about the important risks associated with Tecartus, including cytokine release syndrome (CRS) and serious neurologic adverse reactions, and how to correctly handle and administer Tecartus to ensure product viability. Use of Tecartus is restricted to physicians experienced in the treatment of haematological cancers who have been trained on the RMMs during the site qualification process or annual retraining, if applicable. Another key risk mitigation measure is to ensure hospitals or clinics treating patients with Tecartus have immediate access on-site to tocilizumab to manage the risk of CRS.

The rationale of conducting the survey is to measure the effectiveness of the additional RMMs for Tecartus, as described in the Risk Management Plan (RMP), version 1.0, dated 09 October 2020; specifically, to conduct a survey to measure knowledge and understanding of the key messages in the HCP-directed additional RMMs and Summary of Product Characteristics (SmPC) for Tecartus, including how to mitigate the risks of CRS and serious neurologic adverse events (AEs) and how to correctly handle and administer the Tecartus to ensure product viability.

The survey will be administered to HCPs who work at hospitals and associated clinics who have received training on the additional RMMs and prescribe, handle, dispense, or administer Tecartus or manage Tecartus-related adverse drug reactions (AEs). The survey will assess HCPs knowledge of the risks of Tecartus and its mitigation strategies, as outlined in the routine and additional RMMs.

6. RESEARCH QUESTION AND OBJECTIVE

The primary objective of the study is to measure the 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 SmPC for Tecartus, including how to mitigate the risks of CRS and serious neurologic AEs, and appropriately handle and administer Tecartus.

To meet this objective, the HCP survey will:

- Measure HCPs knowledge of known important identified risks associated with Tecartus
- Assess whether HCPs understand how to identify and treat CRS or serious neurologic AEs
- Assess whether the relevant HCPs understand the correct way of handling and method of administration of Tecartus to maintain product viability
- Assess whether HCPs are aware of the PAC, distribute the PAC, and inform patients about the PAC's content

7. RESEARCH METHODS

7.1. Study Design

The study is a non-interventional, cross-sectional survey of HCPs based in Europe.

The survey will be conducted ≥ 12 months after Tecartus has been introduced in Europe. The survey will be distributed to HCPs who have received training on additional RMMs and prescribe, handle, dispense, or administer Tecartus or manage patients experiencing Tecartus-related AEs, which will ensure these selected HCPs have been trained on the educational materials ≥ 6 months prior to completing the survey as part of the site qualification process or annual retraining, if applicable. The survey will be open for 6 months and the minimum number of completed surveys is expected to be 100. The survey will be conducted in countries where Tecartus was launched, including the Czech Republic, France, Germany, Great Britain, Italy, the Netherlands, Poland, Portugal, and Spain. In addition, these countries contain sites that have undergone a site qualification process, which includes HCPs receiving training on the additional RMMs contained in the Europe RMP for Tecartus.

7.1.1. Survey Design

HCPs may be invited to participate in the study by email, or by postal mail. HCPs will be invited to participate on a volunteer/"opt in" basis. Survey reminders will be sent during the survey recruitment period. Survey data will be collected in each local language through self-administered internet-based surveys.

7.1.2. Pretesting of the Survey

The survey will undergo cognitive pretesting in up to 10 HCPs who prescribe, handle, dispense, or administer Tecartus or manage Tecartus-related AEs. Pretesting will be performed to identify any survey questions that require clarification or revision based on areas of confusion or miscomprehension to avoid potentially negative study results based on misunderstood or poorly worded questions.

Pretesting will be completed in Great Britain, with updates made to the Great Britain base language questionnaire. Following this, the pretested Great Britain base language questionnaire will be forward and back translated in all additional local languages. The local Gilead affiliate will review the translated questionnaires to ensure alignment with local medical and RMM terminology and local demographics (eg, specialities may differ).

Based on the results of the qualitative testing, the questions for the survey may be revised accordingly.

7.2. Setting

The survey questionnaire will collect data from HCPs from qualified sites in Europe who prescribe, handle, dispense, or administer Tecartus or manage patients experiencing Tecartus-related AEs. The target group includes HCPs involved in the preparation of Tecartus for administration and patient care.

Two trainings with slightly different, but usually overlapping target audiences are conducted at sites: the identification and management of CRS and serious neurological AEs, and the guide for handling and method of administration. The different audiences will depend on the HCPs key responsibilities, ie, pharmacists for dispensing, nurses for management of AEs, and physicians for prescribing Tecartus and management of AEs.

Inclusion Criteria

1) Is an HCP who has received training on the educational materials and prescribes, dispenses, handles, or administers Tecartus or manages patients experiencing Tecartus-related AEs.

Exclusion Criteria

1) Is an HCP who has participated in qualitative pretesting of the Tecartus survey

2) Is an HCP who has confirmed that they or any of their immediate family members have ever directly worked for Kite, Gilead, ICON plc, or the EMA

7.3. Variables

The survey will be conducted once in each of the participating sites where HCPs have been trained on the additional RMMs. The study questionnaire is designed to collect the following information:

- Measure HCP's knowledge of known important identified risks associated with Tecartus
- Assess whether HCPs understand how to identify and treat CRS or serious neurologic AEs
- Assess whether the relevant HCPs understand the correct way of handling and method of administration of Tecartus to maintain product viability
- Assess whether the relevant HCPs are aware of the PAC, distribute the PAC, and inform patients about the PAC's content

Responder demographic variables will include medical specialty, practice setting, and country. These will also include in which capacity the HCP works and whether they are prescribing, handling, dispensing or administering Tecartus, and/or managing patient care and Tecartus-related AEs.

7.4. Data Sources

The data source for the survey will be HCPs who received training on the additional RMMs during the site qualification process or annual retraining, if applicable.

The survey will be open for 6 months from the launch date. The minimum number of completed surveys is 100, which is anticipated to occur within 6 months of launching the survey. If 100 completed surveys are not received within 6 months of launch, contingency plans will be implemented, which may include extending the survey timeline by an additional 6 months, inviting additional HCPs who were trained after 30 September 2021 (the training cutoff date for the survey), and outreach via a different modality. This approach will positively impact the potential respondent uptake, as 3 months is adequate time to distribute initial invitations plus up to 2 reminders for participation (if needed).

To date, approximately 1,400 HCPs have been trained on the additional RMMs developed for Tecartus across the target countries. Gilead aims to send the survey to all HCPs in the target countries trained on the additional RMMs, which is assumed to be approximately 2,000 HCPs. As a result, the final survey response will be a sample of all the HCPs trained on the additional RMMs. Although the true response rate is unknown, for purposes of recruitment planning, a response rate of 5% is assumed. A meta-analysis of data from 23 HCP surveys reported a pooled estimated response rate of 2.1% (95% CI: 2.1-2.2) based on the fixed effects model, or 4.7% (95% CI: 3.0-6.6) based on the random effects model {Artime 2019}. Based on this and recent in-house experience where the response rate for completed surveys was 7.6%, invitations to participate in this survey will be sent to at least 2,000 HCPs to achieve a minimum of 100 completed surveys.

7.5. Study Size

The minimum number of completed surveys is 100. Table 7-1 shows the margins of error for the different numbers of responders and different rates of respondents' knowledge. With a minimum of 100 responders and the observed value of HCPs knowledge of 80%, the true value is estimated to lie within the margin of 72.2% to 87.8%.

Table 7-1. Precision and 95% Confidence Intervals for Various Combinations of Sample Size and Knowledge Rates

	60%		70%		80%		90%	
Sample Size	**Precision (%)**	**95% CI**	**Precision (%)**	**95% CI**	**Precision (%)**	**95% CI**	**Precision (%)**	**95% CI**
30	17.5	42.5-77.5	16.4	53.6-86.4	14.3	65.7-94.3	10.4	79.6-100
40	15.2	44.8-75.2	14.2	55.8-84.2	12.4	67.6-92.4	9.3	80.7-99.3
50	13.6	46.4-73.6	12.7	57.3-82.7	11.1	68.9-91.1	8.3	81.7-98.3
60	12.4	47.6-72.4	11.6	58.4-81.6	10.1	69.9-90.1	7.6	82.4-97.6
100	9.6	50.4-69.6	9.0	61.0-79.0	7.9	72.1-87.9	5.9	84.1-95.9

7.6. Data Management

The survey will be self-administered via Confirmit, a web-based survey platform specifically designed for the creation and delivery of multi-lingual surveys. Participants will receive specific access codes to enable them to enter their data. The data entry system will be made available for the time period as noted in Section 7.4, after which time the system will be closed for data entry and the data extracted and analysed. Survey data collected will be stored at secure servers and will be maintained to ensure compliance with applicable local and national regulations. Study data and documents will be retained for 15 years per Gilead data retention policy.

7.7. Data Analysis

Responses to questions for all completed surveys will be analysed using descriptive statistics (count, ranges, proportions, and scores). HCPs knowledge will be evaluated and expressed as proportions or scores. The results will be presented overall, as well as by country and HCP specialty where sample size allows. Categorical variables will be described by the number and proportion in each category. Frequency point-estimates with 2-sided 95% confidence intervals using the binomial distribution (eg, Wald or Clopper-Pearson method, as appropriate) will be constructed to describe the proportion of HCPs aware of the specified risks.

Key questions within the survey were identified as being essential to measure HCPs knowledge of the additional RMMs. Given the complexity of some of the key messages included in the Tecartus RMMs, an acceptable level of knowledge on these essential questions is set at 80%.

Key questions are defined as follows:

- All HCPs: Block 1 #8 (% yes, when applicable).
- HCPs who dispense, handle or administer Tecartus: Block 2 #1 A, B, E, G, H, I
- HCPs who prescribe or manage AEs related to Tecartus: Block 3 #1 A, B, C, D, F, H, I, K, L, M, N, O, P, #2, #3 and #4.

The amount of missing data for each variable will be reported. Data will be presented by means of summary tables. The numbers of invitees, respondents, and non-responders will be recorded, and the response rates will be reported overall, by country, by HCP responsibility, and by HCP speciality. Gilead will compare the above listed characteristics in the targeted HCP population to the final survey sample to describe any differences in the non-responding population.

If sufficient sample size the characteristics for responders and non-responders will be compared based on country and HCP specialty. A detailed statistical analysis plan will be drafted to describe the analyses to be performed. Data from all respondents will be included in the analysis and final report.

7.8. Quality Control

The electronic data entry system will require respondents to answer certain questions before proceeding to the next in order to ensure that surveys are completed as fully as possible. Use of an electronic system will also prevent HCPs going back and amending answers to earlier questions. This method will result in an unbiased evaluation of knowledge retained from the formal training, as subsequent questions in the survey can inform responses to previous questions. The data will be stored on a secure network drive or secure and validated cloud-based data storage system, with access to authorised personnel only from the study team and their delegates.

7.9. Limitations of the Research Methods

These surveys may be limited by social desirability bias if HCPs are hesitant to admit their lack of awareness of the specified risk {Mazzaglia 2018}. The survey instruments will be designed with the intention of minimising this possible bias. Moreover, in a web-based survey of 3,625 HCPs conducted under the Strengthening Collaborations for Operating Pharmacovigilance in Europe joint action initiative, a range of 21% to 97% of HCPs reported familiarity with risk communication materials such as educational measures and Dear HCP Communications. This suggests that HCPs may be comfortable providing truthful responses to this type of question, even if possibly "socially undesirable" {de Vries 2017}.

Random sampling will not be feasible for these surveys, and nonresponse is a common problem in observational studies. However, the study will attempt to obtain as representative a sample as possible and will issue up to 2 reminders per non-respondent to reduce non-response. The characteristics of non-respondents will be compared to the responding population and the potential influence of any differences described as part of the summary of results.

The surveys will be administered online for respondents in all countries but may exclude participants who are less comfortable completing internet surveys. However, the number of respondents who are uncomfortable completing internet surveys is expected to be low, and paper surveys would produce a larger respondent burden, which is expected to deter participation.

Because of the RMP requirement that HCPs must be trained before engaging with Tecartus, the survey is unable to assess knowledge both before and after training on the additional RMMs or change in knowledge as a result of the training on the additional RMMs.

7.10. Other Aspects

Every effort will be made to ensure that the study is completed. Gilead will only terminate the study if there is sufficient cause following consultation with the Pharmacovigilance Risk Assessment Committee. Should this be necessary, Gilead will arrange discontinuation procedures and notify the appropriate regulatory authorities in accordance with local legislation.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Good Pharmacoepidemiology Practices

The study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices, Heads of Medicines Agencies Good Pharmacovigilance Practices (GVP), and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, including archiving of essential documents.

8.2. Independent Ethics Committee Review

The study will not collect patient-level data. All national and Europe regulations will be followed regarding the requirement for Independent Ethics Committee review and approval of the study.

8.3. Informed Consent

Each survey participant will be asked to provide consent to use their responses to the questions for the purposes of the study. Each survey participant's confidentiality will be protected and only reported to Gilead if the participant reports safety information and provides permission to be contacted for follow-up by Gilead.

8.4. Confidentiality

The collected data will not contain participant identifiable fields.

9. MANAGEMENT AND REPORTING OF AEs/ADVERSE REACTIONS

9.1. AEs, Adverse Drug Reactions, and Special Situation Reports

The objective of the study is to measure the awareness and knowledge of additional RMMs of 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 SmPC for Tecartus, including how to mitigate the risks of CRS and serious neurologic AEs. The study design is observational in nature and does not evaluate safety in individual patients. AEs will not be solicited in this observational study. In the event that AEs are incidentally reported during the study, reporting of these AEs will be done by the clinical research organization (CRO) and sent to Gilead Global Patient Safety (GLPS) within 24 hours of awareness by Gilead and/or the CRO to Gilead GLPS by email: Safety_FC@gilead.com or fax: + 1-650-522-5477 or report to local regulatory authority. These AEs will be collected and reported to the regulatory agencies in accordance with standard safety reporting procedures and regulations. All study data will be reported in aggregate form only.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

10.1. Study Report and Publications

A final study report will be prepared and provided to the applicable regulatory agencies. Gilead will ensure that the report meets the standards set out in the Guideline on GVP Module VIII. The final study report will be submitted within 12 months of the end of data collection.

Future publications in the form of abstracts and manuscripts have not been planned to date. Gilead will share with the EMA the final manuscript within 2 weeks after first acceptance for publication.

Once study results are available, any gaps in HCPs knowledge identified in the study for key risks will be re-emphasised to Tecartus-qualified sites during annual retraining (as applicable).

11. REFERENCES

Artime E, Qizilbash N, Garrido-Estepa M, Vora P, Soriano-Gabarro M, Asiimwe A, et al. Are risk minimization measures for approved drugs in Europe effective? A systematic review. Expert Opin Drug Saf 2019;18 (5):443-54.

de Vries ST, van der Sar MJM, Cupelli A, Baldelli I, Coleman AM, Montero D, et al. Communication on Safety of Medicines in Europe: Current Practices and General Practitioners' Awareness and Preferences. Drug Saf 2017;40 (8):729-42.

Mazzaglia G, Straus SMJ, Arlett P, da Silva D, Janssen H, Raine J, et al. Study Design and Evaluation of Risk Minimization Measures: A Review of Studies Submitted to the European Medicines Agency for Cardiovascular, Endocrinology, and Metabolic Drugs. Drug Saf 2018;41 (2):191-202.

12. APPENDICES

Appendix 1. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Checklist for Study Protocols

Study Title: Tecartus Survey: Quantitative Testing of Health Care Professional Knowledge About Tecartus Risk Minimisation

EU PAS Register number: TBD
Protocol identification: KT-EU-472-5966

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for:				
1.1.1 Start of data collection[1]	☒	☐	☐	4
1.1.2 End of data collection[2]	☒	☐	☐	4
1.1.3 Progress report(s)	☐	☐	☒	NA
1.1.4 Interim report(s)	☐	☐	☒	NA
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	4
1.1.6 Final report of study results.	☒	☐	☐	4

Comments:

N/A

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	5
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, or an emerging safety issue)	☒	☐	☐	5
2.1.2 The objective(s) of the study?	☒	☐	☐	6
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

N/A

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	7.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	7.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9

Comments:

The objective of the survey is to assess the HCPs knowledge of known important risks associated with Tecartus. No hypothesis will be tested.

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	7
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☐	☒	☐	
	4.2.2 Age and sex	☐	☒	☐	
	4.2.3 Country of origin	☒	☐	☐	7
	4.2.4 Disease/indication	☒	☐	☐	7
	4.2.5 Duration of follow-up	☒	☐	☐	7
4.3	Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	7

Comments:

N/A

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

This is a cross sectional survey of HCPs

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	7.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	7.7
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

This is a cross sectional survey of HCPs

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	7.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

N/A

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	7
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	7
9.1.3 Covariates and other characteristics?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	7
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	

Section 9: Data sources	Yes	No	N/A	Section Number
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

The data source is the questionnaire responses from HCPs.

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	7.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	7.7
10.3 Are descriptive analyses included?	☒	☐	☐	7.7
10.4 Are stratified analyses included?	☒	☐	☐	7.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	7.7
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Data from the surveys will be summarized descriptively (counts, ranges, proportions, and scores). No measure of association will be estimated.

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	7.6
11.2 Are methods of quality assurance described?	☒	☐	☐	7.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

N/A

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	7.9
12.1.2 Information bias?	☒	☐	☐	7.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	7.5

Comments:

N/A

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	8
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	8

Comments:

N/A

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	3

Comments:

N/A

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	10
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	10

Comments:

N/A

Name of the main author of the protocol: Heribert Ramroth

Date:

Signature:

Appendix 2. Study Acknowledgement

Kite Pharma Inc
2400 Broadway
Santa Monica, CA 90404
UNITED STATES OF AMERICA
TECARTUS SURVEY: QUANTITATIVE TESTING OF HEALTH CARE PROFESSIONAL KNOWLEDGE ABOUT TECARTUS® RISK MINIMISATION
(2.0: 16 FEBRUARY 2022)

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

Heribert Ramroth

Gilead Study Director/Author
Name (Printed)

Signature: Please see subsequent page for Electronic Signature

Date

Anna van Troostenburg

Gilead European Union Qualified Person Responsible for Pharmacovigilance
Name (Printed)

Signature: Please see subsequent page for Electronic Signature

Date

KT-EU-472-5966 Non-Interventional Post-Authorization Safety Study draft Protocol clean v2.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
Anna Vantroostenburg	QPPV eSigned	17-Feb-2022 10:54:51
Heribert Ramroth	Epidemiology eSigned	17-Feb-2022 11:12:08

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1 Multicenter Study Evaluating the Safety and Tolerability of KTE-X19 in Adult Subjects with Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
Protocol Number:	KTE-C19-108 (ZUMA-8)
USAN/INN:	Brexucabtagene Autoleucel/TBD
Company Code:	KTE-X19
IND Number:	16675
EudraCT Number:	2018-001923-38
Clinical Study Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404
Key Sponsor Contacts:	Enrique Granados, MD Sr Medical Director, Clinical Development Phone: +34 628866532 email: Enrique.Granados@gilead.com Krista Goodman Clinical Program Manager, Clinical Operations Phone: 206-256-4901 Email: kgoodman@kitepharma.com
Protocol Version/Date:	Original 15 June 2018 Amendment 1 02 May 2019 Amendment 2 27 May 2020 Amendment 3 01 September 2021

PROTOCOL SYNOPSIS

Kite Pharma, Inc.
2400 Broadway
Santa Monica, CA 90404

Title:	A Phase 1 Multicenter Study Evaluating the Safety and Tolerability of KTE-X19 in Adult Subjects with Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
Indication:	Adult subjects with relapsed or refractory (r/r) chronic lymphocytic leukemia (CLL) and r/r small lymphocytic lymphoma (SLL) who have been previously treated with at least two prior lines of therapy, at least one of which must have included any Bruton's tyrosine kinase (BTK) inhibitor
Study Design:	ZUMA-8 is a Phase 1, multicenter, open-label study evaluating the safety and tolerability of KTE-X19 in adult subjects with r/r CLL and SLL. During the study, approximately 15 to 27 subjects with r/r CLL and SLL will be assessed to evaluate the safety of KTE-X19. A safety review team (SRT) that is internal to the study sponsor, in collaboration with at least 1 study investigator, will review all data available, including safety and efficacy data and make recommendations regarding further enrollment based on the incidence of dose-limiting toxicities (DLTs) and overall safety profile and cell expansion of KTE-X19. See Section 9.7. The trial will separated into two different stages: In the first stage, subjects with r/r CLL will be enrolled using a 6+3 study design into cohorts described below: • **Cohort 1:** Up to 9 subjects will be enrolled at 1 x 10^6 anti-CD19 chimeric antigen receptor (CAR) T cells/kg. Decision to enroll in Cohort 2 will be based on incidence of DLT in Cohort 1. • **Cohort 2**: Up to 9 subjects will be enrolled at 2 x 10^6 anti-CD19 CAR T cells/kg. In the second stage (Amendment 2), subjects with r/r CLL and SLL will be enrolled into Cohort 3 and 4 as described below: • **Cohort 3:** Three (3) subjects with r/r CLL andSLL with ≤ 1% malignant cells in peripheral blood or absolute lymphocyte count (ALC) < 5,000 cells/μL will be enrolled and dosed with KTE-X19 at a dose of 1 x 10^6 anti-CD19 CAR T cells/kg. Subjects must have received at least 2 prior lines of treatment, one of which must include a BTK inhibitor. This is an exploratory cohort. No additional dose levels will be evaluated.

- **Cohort 4**: Up to approximately 15 subjects with r/r CLL who have been previously treated with at least two prior lines of therapy and are receiving ibrutinib as a single agent, or ibrutinib in combination with anti-CD20 antibodies, BCL-2 inhibitors, and PI3k inhibitors as the last line of therapy. Subjects must have received ibrutinib for at least 6 months prior to screening. Ibrutinib administration will continue up to 30 hours prior to leukapheresis. In case of treatment interruption with ibrutinib, the principal investigator should reach out to the medical monitor to discuss. A 3+3 study approach will be used to evaluate two doses of KTE-X19.
  - Cohort 4A:
    - Up to 6 subjects using 3+3 approach will be enrolled and dosed at 1 x 10^6 anti-CD19 chimeric antigen receptor (CAR) T cells/kg. Decision to enroll in Cohort 4B will be based on SRT review of Cohort 4A.
  - **Upon completion of Cohort 4A SRT, it was determined not to enroll subjects in Cohort 4B*.
  - Cohort 4B:
    - Up to 12 subjects will be enrolled and dosed at 2 x 10^6 anti-CD19 chimeric antigen receptor (CAR) T cells/kg.

Once a safe dose is established in Cohort 4, additional subjects will be enrolled and dosed for a total of up to twelve (12) subjects at the safe dose level. The maximum number of subjects enrolled and dosed in Cohort 4 will be approximately 15 subjects.

Each subject will proceed through the following study periods:

- Screening
- Enrollment/Leukapheresis
- Bridging Therapy
- Lymphodepleting/Conditioning chemotherapy
- Investigational product (IP) treatment
- Post-treatment assessment
- Long-term follow-up

For study requirements assigned to each study arm, refer to the schedule of assessments (SOA) and Section 7 for details.

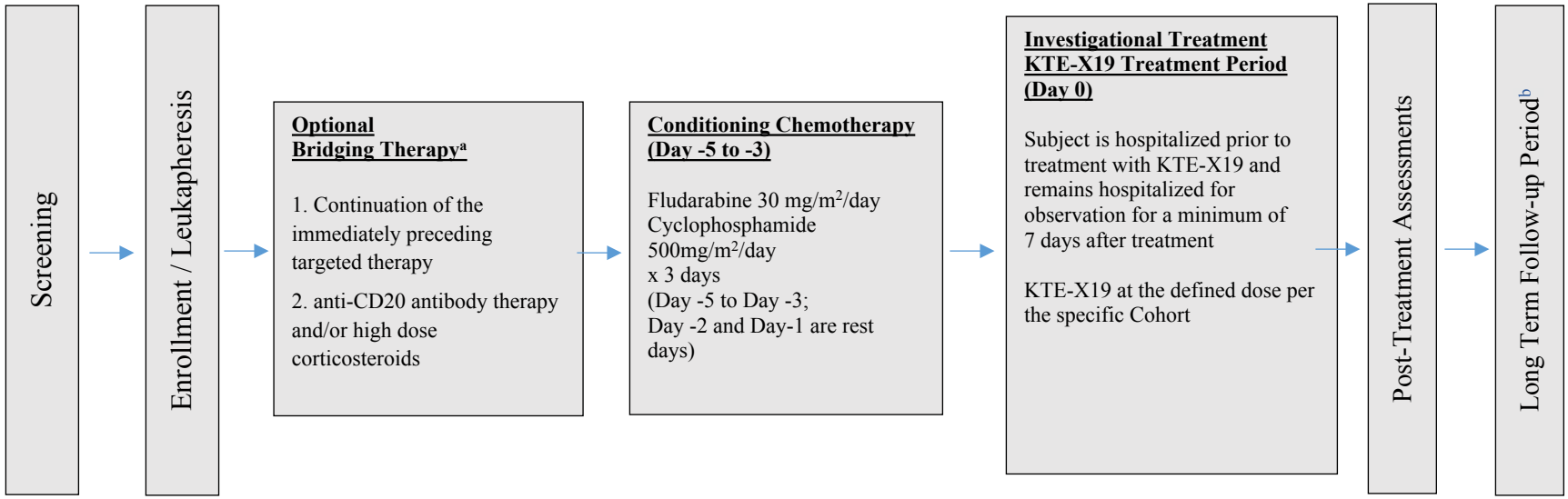
A study schema is provided at the end of the protocol synopsis section.

Study Objectives:	Primary objective of Phase 1: Evaluate the safety and tolerability of KTE-X19 in subjects with r/r CLL and SLL. Secondary objectives are to characterize the safety profile and anti-KTE-X19 antibody, and to evaluate the efficacy of KTE-X19 as measured by the objective response rate (ORR) per investigator review in subjects with r/r CLL treated with KTE-X19. Efficacy analysis for ORR will be performed only for the selected safe dose cohort. Exploratory objectives will evaluate exploratory biomarker, pharmacokinetic, and pharmacodynamic endpoints. For the selected safe dose cohort, the additional efficacy endpoints such as complete response/complete response with incomplete hematopoietic recovery (CR/CRi) rate, minimal residual disease negativity (MRD-) rate, CR/CRi with MRD- rate, the duration of response (DOR), progression-free survival (PFS) and overall survival (OS) might be explored.
Hypothesis:	No formal hypothesis testing for this phase 1 study.
Primary Endpoints:	Incidence of DLTs in subjects treated with KTE-X19 (Section 9.7)
Secondary Endpoint(s):	• ORR (CR/CRi/PR) per investigator review as defined by IWCLL 2018 criteria (Appendix 3) for selected safe dose cohort • Incidence of adverse events (AEs) • Levels of anti-CD19 CAR T cells in blood
Sample Size:	Up to approximately 27 subjects will be enrolled and treated in the study.
Study Eligibility:	See Section 5 for list of all eligibility criteria.
Treatment:	All subjects will receive conditioning chemotherapy followed by the investigational treatment, KTE-X19. At the discretion of the investigator, bridging therapy may be administered prior to conditioning chemotherapy. **Conditioning Chemotherapy** KTE-X19 is administered after a conditioning chemotherapy regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day administered IV over 30 minutes on Day −5, Day −4, and Day −3 prior to KTE-X19 infusion. Day −2 and Day −1 are rest days.

	KTE-X19 KTE-X19 treatment consists of a single infusion of CAR-transduced autologous T cells administered intravenously (IV) at a target dose of 1 x 10^6 or 2 x 10^6 anti-CD19 CAR T cells/kg (Section 3.1). All subjects will be hospitalized to receive KTE-X19 infusion followed by a minimum 7-day observation period. Refer to Section 6.1.4 and Section 7.9.3.2 for treatment details. Refer to Section 6.1.3 and Section 7.9.3 for chemotherapy treatment details.
Bridging Therapy:	At the discretion of the investigator, bridging therapy may be considered for subjects, particularly those with rapidly progressive disease (PD) at screening (see Section 6.1.2). Bridging therapy may consist of: • Continuation of the immediately preceding line of treatment with targeted agent(s) (eg, BTK inhibitors, BCL-2 inhibitors, or PI-3K inhibitors) • Anti-CD20 antibody therapy and/or high dose corticosteroids. Dexamethasone 40 mg or its equivalent is recommended, although the choice, dose, and route of administration of corticosteroid can be adjusted for age and comorbidities per local and institutional guidelines. Corticosterioids at a dose of ≥ 5 mg prednisone (or equivalent) must be avoided for 7 days prior to leukapheresis and 5 days prior to KTE-X19 administration. Bridging therapy may be administered after leukapheresis and must be discontinued 48 hours prior to administration of conditioning chemotherapy. Subjects should be restaged after the end of the bridging therapy and prior to start of conditioning chemotherapy.
Procedures:	At specific time points as outlined in the SOA, subjects will undergo the following procedures: collection of informed consent; general medical history, including previous treatments for CLL and SLL; physical exam, including vital signs and Eastern Cooperative Oncology Group (ECOG) performance status; local blood draws for complete blood count (CBC), chemistry panels**,** lactate dehydrogenase (LDH), C-reactive protein, ferritin; central blood draws for cytokines, lymphocyte subsets, antibodies to anti-CD19 CAR T cells, replication-competent-retrovirus (RCR), and anti-CD19 CAR T cell analysis. Women of childbearing potential will undergo a urine or serum pregnancy test.

	Subjects will also undergo a baseline electrocardiogram (ECG), echocardiogram (ECHO/MUGA), diagnostic computed tomography(CT) scan (preferred) or magnetic resonance imaging (MRI) of the head, neck, chest, abdomen, and pelvis, bone marrow aspirate and biopsy, optional nodal biopsy, and leukapheresis. Routinely throughout the conduct of the study, all subjects will be asked to report concomitant therapies, AEs, and subsequent CLL andSLL therapy. Subjects will undergo neurological assessment. For details for all study requirements, refer to Section 7 and the SOAs.
Statistical Considerations:	The primary endpoint for the Phase 1 portion of the study is incidence of DLTs in subjects treated with KTE-X19. A 6 + 3 dose escalation/de-escalation plan was used in the Cohort 1 and Cohort 2 DLT evaluation period. Amendment 2 will use a 3 + 3 dose escalation plan for Cohort 4. Cohort 3 is an exploratory cohort. For the selected safe dose cohort, the ORR (CR/CRi/PR) will be calculated for mITT analysis set. A 95% confidence interval will be provided by Clopper-Pearson method. The mITT set is defined as all subjects treated with KTE-X19 and with radiographically measurable disease after completion of bridging therapy (if applicable) and prior to administration of conditioning chemotherapy.

Figure 1. Study Schema



a Bridging therapy may be administered after leukapheresis and can consist of:
1. Continuation of the immediately preceding line of treatment with targeted agent(s) (eg, BTK inhibitors, BCL-2 inhibitors, or PI-3K inhibitors)
2. Anti-CD20 antibody therapy and/or high dose corticosteroids. Dexamethasone 40 mg or its equivalent is recommended though the choice, dose and route of administration of corticosteroid can be adjusted for age and comorbidities per local and institutional guidelines. Corticosteroids at a dose of ≥5mg prednisone (or equivalent) must be avoided for 7 days prior to leukapheresis and 5 days prior to KTE-X19 administration.

Bridging therapy must be discontinued prior to administration of conditioning chemotherapy. Refer to Section 6.1.2 for details.

b After the end of KTE-C19-108, subjects who received an infusion of KTE-X19 will complete the remainder of the 15-year follow-up assessments in a separate long-term follow-up study, KT-US-982-5968.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	Adverse event
ALC	Absolute lymphocyte count
BCL-2	B-cell lymphoma 2
BR	Bendamustine and rituximab
BTK	Bruton's tyrosine kinase
CAR	Chimeric antigen receptor
CBC	Complete blood count
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRi	Complete response with incomplete hematopoetic recovery
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
DLT	Dose-limiting toxicity
ECHO	Echocardiogram
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FAS	Full analysis set
FCR	Fludarabine cyclophosphamide, and rituximab
GCP	Good Clinical Practice
GVHD	Graft-versus-host disease
HEENT	Head, ears, eyes, nose, and throat
HLH	Hemophagocytic lymphohistiocytosis
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Hamonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	Investigational product
IPM	Investigational Product Manual
IRB/IEC	Institutional Review Board/Endependent Ethics Committee
ITK	IL-2-inducible T-cell kinase
IV	Intravenous

IWCLL	International Workshop on Chronic Lymphocytic Leukemia
KI	Kinase inhibitor
LP	Lumbar puncture
LVEF	Left ventricular ejection fraction
LTFU	Long-term Follow-up
mITT	Modified intend to treat
MRI	Magnetic resonance imaging
MRD	Minimal residual disease
NCI	National Cancer Institute
OS	Overall survival
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PFS	Progression-free survival
PI-3K	Phosphoinositide 3-kinase inhibitor
PK	Pharmacokinetic(s)
PR	Partial response
r/r	Relapsed/refractory
RCR	Replication-competent retrovirus
SAE	Serious adverse event
scFv	Single chain variable fragment
SCT	Stem cell transplant
SLL	Small lymphocytic lymphoma
SOA	Schedule of assessments
SOC	Standard of care
SRT	Safety review team
TEAEs	Treatment emergent adverse events
Tcm	Central memory T cells
Treg	Regulatory T cells
WBC	White blood cell

1. OBJECTIVES

1.1. Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of KTE-X19 in subjects with relapsed or refractory (r/r) chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

1.2. Secondary Objectives

Secondary objectives are to characterize the safety profile and anti-KTE-X19 antibodies, and to evaluate the efficacy of KTE-X19 as measured by the objective response rate (ORR) per investigator review in subjects with r/r CLL treated with KTE-X19. Efficacy analysis for ORR will be performed only for the selected safe dose cohort.

1.3. Exploratory Objectives

Exploratory objectives are to characterize the safety profile and endpoints including complete response (CR)/CR with incomplete hematopoietic recovery (CRi) rate, minimal residual disease negativity (MRD-) rate, CR/MRD rate, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and to evaluate biomarkers, pharmacokinetic (PK) analysis, and pharmacodynamic markers of CAR T-cell function, immune activation, and alloimmunization. Available nodal biopsies will be used to investigate levels of B-cell markers (eg CD19, CD20) and attributes of the tumor microenvironment (e.g. levels of T-cell infiltration). Efficacy analysis endpoints listed will only be explored for the selected safe dose cohort.

2. DISEASE BACKGROUND

2.1. CLL and SLL Disease Background

CLL is the most commonly occurring leukemia in Europe and the United States (US) with an estimated lifetime risk of 1:167 {Sant 2010, Surveillance Epidemiology and End Results (SEER) Program 2011}. CLL is marked by the progressive accumulation of functionally impaired monoclonal B lymphocytes in blood, bone marrow, lymph nodes, spleen, and liver {Hallek 2018, Rozman 1995}. Symptoms include fever, night sweats, and weight loss, and disease progression is often accompanied by lymphadenopathy, splenomegaly, or hepatomegaly. CLL is most commonly a disease of the elderly, as 70% of patients are ≥ 65 years at diagnosis, and the median age is 72 years {Surveillance Epidemiology and End Results (SEER) Program 2011}. Patients harboring a deletion of the short arm of chromosome 17 (del17p) or an inactivating mutation in the TP53 gene (TP53mut) are considered to be high-risk and have worse survival outcomes than patients who do not harbor these mutations {Hallek 2019}.

CLL and small lymphocytic lymphoma (SLL) are different manifestations of the same disease. SLL are the less frequent nonleukemic cases of CLL, where lymph node involvement is prevalent, in the absence of cytopenias caused by a clonal bone marrow infiltrate, and with $< 5 \times 10^9$/L B lymphocytes in the peripheral blood {Tsimberidou 2007}. The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with $< 5 \times 10^9$/L B lymphocytes in the peripheral blood. In SLL, the diagnosis should be confirmed by histopathology evaluation of a lymph node biopsy. SLL follows the same management guidelines as CLL {Scarfo 2016}. The indolent clinical behavior of SLL has often led to the approach of deferring treatment in asymptomatic patients until progressive disease (PD) becomes evident.

For the treatment of CLL and SLL, chemoimmunotherapy remains an option, particularly as an initial treatment, for those who are considered to be fit and of favorable-risk. The CLL8 and CLL10 studies of the German CLL group established the benefit of adding an anti-CD20 monoclonal antibody to chemotherapy and the value of the fludarabine, cyclophosphamide, and rituximab (FCR) and bendamustine and rituximab (BR) regimens for the treatment of CLL {Eichhorst 2016, Hallek 2010}. The CLL11 study subsequently demonstrated improved outcomes with the third generation anti-CD20 antibody obinutuzumab in combination with chlorambucil compared with rituximab-chlorambucil and chlorambucil monotherapy {Goede 2014}. For the overwhelming majority of patients, these treatments are not curative; the disease eventually relapses, necessitating further intervention to establish and maintain tumor control. While chemoimmunotherapy can be pursued at the time of relapse, it is associated with toxicity, including myelosuppression and fatigue. Patients who relapse after an initial remission duration ≥ 3 years after frontline FCR are considered suitable to receive FCR again as the first salvage therapy. Salvage treatment offers limited benefit for patients with a limited depth of response to initial therapy or those who have recurrent disease within 3 years {Tam 2014}. Patients with del17p or TP53mut are particularly poorly served by chemoimmunotherapy irrespective of treatment history.

Small molecule targeted agents have transformed the treatment landscape for CLL, largely supplanting chemoimmunotherapy, but these agents require chronic administration. One such agent is ibrutinib, a first-in-class irreversible inhibitor of Bruton's tyrosine kinase (BTK) that is approved for the treatment of both previously untreated and r/r CLL. In the r/r setting, it results in a high objective response rate (ORR) (> 80%) when used in combination with a BR regimen, but a limited depth of response (< 22% CR/CRi) {Chanan-Khan 2016}. Among those who progress on ibrutinib, a significant proportion of patients develop high-risk disease and have poor OS ranging from 3 to 6 months following relapse {Jain 2015, Parikh 2015, Sandoval-Sus 2015}.

A second BTK inhibitor, acalabrutinib, was shown to be efficacious in a Phase 1/2 study of 132 subjects with r/r CLL (2 additional subjects had SLL). After a median follow-up of 19.8 months, the ORR was 85% (93% when including partial response [PR] with lymphocytosis), but the CR rate was 2%. The median PFS and OS were not reached {Byrd 2017}. Acalabrutinib has also shown some promise as a treatment for patients with CLL who are intolerant to ibrutinib and have not yet progressed {Awan 2016}. This treatment would not be suitable for patients who have progressed on ibrutinib or developed BTK mutations. Acalabrutinib has been approved for the treatment of adults with CLL as first line therapy as well as in the r/r setting, based on 2 randomized, actively controlled trials (ELEVATE-TN and ASCEND trials) {CALQUENCE 2019}.

Venetoclax is a first-in-class inhibitor of BCL-2 that is approved for patients with r/r CLL who have del17p and at least 1 prior therapy in the US. Venetoclax was also approved by the FDA in May 2019 for first line treatment for adult patients with CLL or SLL {VENCLEXTA 2019}. Approval was based on CLL14 (NCT02242942), a randomized (1:1), multicenter, open label, actively controlled trial of venetoclax in combination with obinutuzumab (VEN +G) versus obinutuzumab in combination with chlorambucil (GClb) in 432 patients with previously untreated CLL with coexisting medical condition. The major efficacy outcome was progression-free survival (PFS) assessed by an independent review committee. The trial demonstrated a statistically significant improvement in PFS for patients who received VEN+G compared with those who received GClb (HR 0.33; 95% CI: 0.22, 0.51; p<0.0001). Median PFS was not reached in either arm after a median follow-up duration of 28 months. The overall response rate was 85% in VEN+G arm compared to 71% in GClb arm, p=0.0007. The trial also demonstrated statistically significant improvements in rates of minimal residual disease negativity (less than one CLL cell per 10^4 leukocytes) in bone marrow and peripheral blood. Overall survival data were not mature at this analysis. In the European Union (EU), venetoclax is approved for use in combination with rituximab for patients with CLL who have received at least 1 prior therapy, and as a monotherapy in those patients with CLL with del17p or TP53mut who are unsuitable for or have not responded to a B-cell receptor pathway inhibitor and those without del17p/TP53mut who have not responded to both chemoimmunotherapy and a B-cell receptor pathway inhibitor. Approvals for venetoclax monotherapy in the r/r setting were based on 2 single-arm Phase 2 trials that demonstrated high ORRs of 60% to 80% but low CR/CRi rates of < 10% {Jones 2018, Stilgenbauer 2016}. A recent study suggests a high rate of Richter's transformation accompanying progression on venetoclax; in an evaluation of 67 subjects across 3 early phase trials, 17 of 25 subjects who progressed manifested Richter's transformation {Anderson 2017}. Even in the era of targeted agents, outcomes for patients with Richter's transformation remain extremely poor with a median OS of 3.3 months in a recent study of 71 subjects following treatments targeting B-cell receptor kinases or BCL-2 {Davids 2017}. Furthermore, venetoclax

has a significant risk of tumor lysis, particularly for patients with a high disease burden, necessitating careful monitoring during intrapatient dose escalation over the course of 5 weeks at the time of initiation of therapy; patients at a high risk and some at an intermediate risk for tumor lysis may require hospitalization during the initial steps of dose escalation for intensive monitoring.

Idelalisib, a first-in-class inhibitor of the p110δ catalytic subunit of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) signaling enzyme, is also approved for use in combination with rituximab for the treatment of patients with relapsed CLL. The results that led to its approval demonstrated a high ORR of 83.6% in subjects previously treated exclusively with chemoimmunotherapy but a limited depth of response (0 CRs) {ZYDELIG 2016}. Idelalisib has not been studied systematically in CLL following treatment with ibrutinib but the results available suggest significantly decreased efficacy, with an estimated ORR to idelalisib of 28% in 1 retrospective study {Mato 2016}. In a larger multicenter study, a retrospective analysis of 683 CLL patients treated with kinase inhibitors (KIs) or venetoclax was conducted {Mato 2017}. Patients treated with ibrutinib (versus idelalisib) as first KI had a significantly better PFS in all settings (frontline, r/r, del17p, complex karyotype). When these patients failed the initial KI and were treated with an alternate KI or venetoclax, they had superior PFS compared with chemoimmunotherapy. In patients who discontinued ibrutinib due to disease progression or toxicity, outcomes were improved if they received venetoclax (ORR of 79%) compared to idelalisib (ORR of 46%).

Allogeneic hematopoietic stem cell transplantation is a potentially curative treatment option for CLL but is used rarely in the era of targeted therapy, as few patients are good candidates due to age and comorbidities. Further, it is accompanied by a significant non-relapse mortality risk from acute and chronic graft-versus-host disease (GVHD) in the first 2 years following transplant for CLL, approaching 30% in some studies, as well as significant morbidity in at least a quarter of patients who do survive {Dreger 2014}. Thus, allogeneic transplant is an unsuitable option for most patients.

CAR-modified autologous T cells offer the possibility of yielding high response rates and long-term durable responses in CLL without the accompanying morbidity and mortality associated with the conditioning treatment or GVHD that accompanies allogeneic transplant. CD19 is a 95 kDa transmembrane protein expressed exclusively in the B-cell lineage from pro-B cells through mature B cells but not on hematopoietic stem cells or plasma cells {Anderson 1984, Gupta 2009, Lin 2004, Nadler 1983, Uckun 1990, Uckun 1988}. CD19 is expressed in a number of B-cell malignancies, including non-Hodgkin lymphoma, CLL, and B-cell acute lymphocytic leukemia {Anderson 1984, Johnson 2009b, Leonard 2001, Nadler 1983, Olejniczak 2006, Rodriguez 1994, Uckun 1988}. Anti-CD19 CAR T cells have demonstrated high rates of durable responses in patients with r/r acute lymphoblastic lymphoma and diffuse large B-cell lymphoma, and clinical trials are currently underway evaluating the benefit in other non-Hodgkin lymphomas. Although the treatment experience to date for CLL has been more limited, the early experience shows high ORRs (55 to 90%) even in patients previously treated with ibrutinib {Kochenderfer 2012, Kochenderfer 2015, Porter 2015, Siddiqi 2019, Siddiqi 2018, Turtle 2017}. Consistent with a marked depth of response in response to anti-CD19 CAR T cells, a subset of patients demonstrate an absence of disease relapse years following a single treatment.

2.2. KTE-X19

Kite Pharma, Inc. (hereafter referred to as the sponsor), is focused on the development and commercialization of engineered autologous cell therapy products that harness the power of a patient's own immune system to selectively target and eradicate cancer cells. Kite is developing an anti-CD19 CAR T-cell product for treatment of patients with r/r B-cell malignancies that express CD19. CD19 is expressed by most B-cell malignancies {Johnson 2009a, Leonard 2001, Olejniczak 2006, Rodriguez 1994, Uckun 1988} as well as all normal B lymphocytes in peripheral blood and spleen, but not by granulocytes, monocytes, platelets, erythrocytes, and T lymphocytes {Uckun 1988}. Briefly, the anti-CD19 CAR comprises the following domains: an extracellular anti-human CD19 single-chain variable region fragment (scFv); the partial extracellular domain and complete transmembrane and intracellular signaling domains of human CD28, a lymphocyte costimulatory 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. Additional details regarding the mechanism of action of KTE-X19 can be found in the Investigator's Brochure (IB).

The manufacture of KTE-X19 begins with collection of the patient's own T cells via leukapheresis. For subjects with high numbers of circulating tumor cells (eg, those with B-lineage acute lymphoblastic leukemia, CLL, or mantle cell lymphoma), the T cells in the harvested leukocytes undergo a T-cell enrichment step (referred to as the XLP process) that removes circulating tumor cells from the leukapheresis material. Additional details regarding the manufacture of KTE-X19 are provided in the Investigator's Brochure.

2.3. Prior Anti-CD19 CAR T-cell Study Designs and Results

Refer to the current KTE-X19 Investigator's Brochure (IB) for the most current anti-CD19 CAR T-cell nonclinical and clinical information.

3. STUDY DESIGN AND RATIONALE

3.1. General Study Design

KTE-C19-108 (ZUMA-8) is a Phase 1, multicenter, open-label study evaluating the safety and tolerability of KTE-X19 in adult subjects with r/r CLL and SLL will be assessed to evaluate the safety of KTE-X19. The study will enroll up to approximately 27 subjects with r/r CLL and SLLwill be assessed to evaluate the safety of KTE-X19. Two dose levels may be evaluated in the study.

Dose Level	Total anti-CD19 CAR T cells/kg
Starting Dose	1 x 10^6
Escalating Dose	2 x 10^6

During the study, approximately 15 to 27 subjects with r/r CLL and SLL will be assessed to evaluate the safety of KTE-X19. A safety review team (SRT) that is internal to the study sponsor, in collaboration with at least 1 study investigator, will review all data available, including safety and efficacy data and make recommendations regarding further enrollment based on the incidence of DLTs and overall safety profile and cell expansion of KTE-X19. See Section 9.7.

The trial will be separated into two different stages:

In the first stage, subjects with r/r CLL will be enrolled using a 6+3 study design into cohorts described below:

- **Cohort 1:** Up to 9 subjects will be enrolled at 1 x 10^6 anti-CD19 chimeric antigen receptor (CAR) T cells/kg. Decision to enroll in Cohort 2 will be based on incidence of DLT in Cohort 1.

- **Cohort 2**: Up to 9 subjects will be enrolled at 2 x 10^6 anti-CD19 CAR T cells/kg.

In the second stage (Amendment 2), subjects with r/r CLL and SLL will be enrolled into Cohort 3 and 4 as described below:

- **Cohort 3:** Three (3) subjects with r/r CLL and SLL with ≤ 1% malignant cells in peripheral blood or absolute lymphocyte count (ALC) < 5,000 cells/µL will be enrolled and dosed KTE-X19 at a dose of 1 x 10^6 anti-CD19 CAR T cells/kg. This is an exploratory cohort. No additional dose levels will be evaluated.

- **Cohort 4**: Up to approximately 15 subjects with r/r CLL who have been previously treated with at least two prior lines of therapy and are receiving ibrutinib as a single agent, or ibrutinib in combination with anti-CD20 antibodies, BCL-2 inhibitors, and PI3k inhibitors as the last line of therapy. Subjects must have received ibrutinib for at least 6 months prior to

screening. Ibrutinib administration will continue up to 30 hours prior to leukapheresis. In case of treatment interruption with ibrutinib, the principal investigator should reach out to the medical monitor to discuss. A 3+3 study approach will be used to evaluate two doses of KTE-X19.

— Cohort 4A:

- Up to 6 subjects using 3+3 approach will be enrolled and dosed at 1 x 10^6 anti-CD19 chimeric antigen receptor (CAR) T cells/kg. Decision to enroll in Cohort 4B will be based on incidence of DLT in Cohort 4A.
- **Upon completion of Cohort 4A SRT, it was determined not to enroll subjects in Cohort 4B.*

— Cohort 4B:

- Up to 6 subjects will be enrolled and dosed at 2 x 10^6 anti-CD19 chimeric antigen receptor (CAR) T cells/kg (escalating dose)

Once a safe dose is established in Cohort 4, additional subjects will be enrolled and dosed for a total of up to twelve (12) subjects at the safe dose level (including those who were enrolled during the SRT evaluation phase). The maximum number of enrolled and dosed in Cohort 4 will be approximately 15 subjects.

Each subject will proceed through the following study periods:

- Screening
- Enrollment/Leukapheresis
- Bridging therapy period
- Lymphodepleting/conditioning chemotherapy
- Investigational product (IP) treatment
- Post-treatment assessment
- Long-term follow-up. After the end of KTE-C19-108, subjects who received an infusion of KTE-X19 will complete the remainder of the 15-year follow-up assessments in a separate Long-term Follow-up study (LTFU), KT-US-982-5968.

For study requirements, refer to the schedule of assessments (SOA), Table 3 and Table 4, and Section 7 for details.

A study schema is included at the end of the protocol synopsis (Figure 1).

3.2. Study Rationale For Cohort 1 and Cohort 2

While chemoimmunotherapy and targeted therapy represent efficacious treatment options for CLL, very few patients are cured by currently available treatment short of allogeneic stem cell transplant, which is itself limited by treatment-associated morbidity and mortality. Since its approval, ibrutinib has become widely used in both previously untreated patients with CLL as well as those with r/r disease.

Second generation BTK inhibitors, such as acalabrutinib, have demonstrated activity in r/r CLL patients who have not progressed with prior ibrutinib treatment or in patients who have become intolerant to ibrutinib{Awan 2016}. Acalabrutinib has been approved for the treatment of adults with CLL as first line therapy as well as in the r/r setting, based on 2 randomized, actively controlled trials (ELEVATE-TN and ASCEND trials) {CALQUENCE 2019}.

Patients who have progressed or are ineligible to receive a BTK inhibitor due to toxicity may have limited options that can offer deeper responses. While venetoclax is approved for previously treated CLL, it shows limited depth of response in this setting with an accompanying significant risk of tumor lysis syndrome and a high rate of progression with Richter's syndrome. Idelalisib has not been studied systematically following ibrutinib treatment though some retrospective analyses suggest limited efficacy. Furthermore, chronic treatment with these approved targeted agents is necessitated by the absence of deep responses or significant rates of MRD−. As treatment with these agents has become more prevalent, the limitations of their accompanying toxicity have also become more evident; treatment discontinuations due to AEs occur in a significant subset of patients {Maddocks 2015, Mato 2018}.

Engineered autologous cell therapy has the potential to yield long lasting durable responses following a single administration. Autologous CAR T cells targeted to CD19 have transformed the treatment landscape for r/r diffuse large B-cell lymphoma and acute lymphocytic leukemia and are under evaluation for a number of additional B-cell malignancies. Early results with anti-CD19 CAR T cells from the National Cancer Institute, University of Pennsylvania, and the Fred Hutchinson Cancer Research Center have demonstrated efficacy in CLL with a tolerable safety profile.

This study will evaluate the safety and tolerability of KTE-X19 in subjects with r/r CLL and SLL who have failed or have become intolerant to a BTK inhibitor.

3.2.1. Rationale for Cohort 3

In this cohort, the sponsor will explore if enrollment of subjects with a diagnosis of r/r SLL or r/r CLL who present with ≤ 1% circulating tumor cells (low tumor burden) in peripheral blood demonstrate meaningful CAR T-cell expansion. One subject enrolled in ZUMA-8 Cohort 1 who presented with a low circulating tumor burden achieved meaningful expansion of CAR T cells and a PR (Data on File). The published experience from the NCI of 8 subjects with r/r CLL treated with anti-CD19 CAR-transduced T cells (using the same construct used in this study) demonstrated a robust expansion of CAR T cells in subjects who had low circulating CLL burden with a median pre-apheresis ALC of 0.54 x 10^3 cells/uL.

A phase 1 study conducted at Memorial Sloan Kettering Cancer Center, investigated CD-19-targeted CAR T-cells incorporating a CD28 costimulatory domain {Geyer 2019}. The study included 16 patients with r/r CLL. The analysis of disease burden (absolute lymphocyte counts) of these patients at the time of CAR T-cell infusion, showed a median value of 2.35 x 10^3 cells/uL, which is lower compared with the median value of 7.2 x 10^3 cells/uL found in 10 subjects dosed with KTE-X19 in ZUMA-8 study, cohorts 1 and 2.

3.2.2. Rationale for Cohort 4 {Geyer 2019}

3.2.2.1. Introduction

Only 10 to 30% of CLL patients treated with chemoimmunotherapy or targeted therapies achieve CR or MRD^-, and 50% of these patients relapse within 3 to 4 years {Bottcher 2012, Strati 2014}. Patients who progress on targeted agents have limited options and shortened OS {Anderson 2017, Mato 2016}.

Initial clinical trials with CAR T cells in r/r CLL aimed to address the feasibility and proof of concept of monotherapy with CAR T cells targeting the pan-B-cell marker CD19. Early clinical results showed ORR of 71% in this heavily pretreated patient population {Turtle 2017}. The immune dysregulation observed in patients with CLL is well characterized, and intrinsic T-cell defects impose a significant barrier to both the feasibility of generating CAR T cells and the responsiveness of the disease to CAR T-cell-based therapy. One of the most critical determining factors for the success of CAR T cells is the expansion and persistence of antigen-specific T cells {Robbins 2004}. Additionally, the response of CLL to CAR T-cell therapy is influenced by the composition of the cellular product and/or T-cell fitness {Fraietta 2018}.

The following preclinical and clinical data are intended to support the rationale of including Cohort 4 in this study, in which subjects must have been exposed to ibrutinib for at least 6 months prior to screening, to test if this exposure prior to leukapheresis has a positive impact on T-cell fitness, with the goal of increasing expansion of CAR T cells through ibrutinib's modulatory effect on T-cell function.

3.2.2.2. Preclinical Data

Ibrutinib exerts its immunomodulatory effects by inhibiting BTK and IL-2 inducible T cell kinase (ITK) signaling. Peripheral blood mononuclear cells (PBMC) from 19 subjects with CLL treated with ibrutinib were evaluated for T-cell phenotype, immune function, and CLL cell immunosuppressive capacity. Results showed that ibrutinib treatment increased in vivo persistence of activated T cells, decreased the Treg/$CD4^+$ T-cell ratio, and diminished the immune-suppressive properties of CLL cells through BTK-dependent and independent mechanisms {Long 2017}. It was demonstrated that the influence of ibrutinib in subjects with CLL also has a direct positive influence on the immunosuppressive capacity of the primary tumor cells, reducing the expression of the immunosuppressive molecules CD200 and BTLA as well as IL-10 production by CLL cells {Long 2017}.

In addition, ibrutinib, through ITK inhibition, enables pleotropic effects on the various T-cell subsets including enhancing expansion of activated T cells, while having no deleterious effects on the central memory T cells (Tcm) or naïve T cells; no collateral expansion of the regulatory T cells (Treg cells); and partially reversing the exhausted T-cell phenotype by reducing the expression of PD-1 and CTLA4 {Long 2017}. Preclinical evidence demonstrated that ibrutinib, when administered concurrently with CAR T cells, improves CAR T-cell engraftment, tumor clearance, and survival in human xenograft models of acute lymphocytic leukemia and CLL {Fraietta 2016}. Specifically, treatment with ibrutinib for ≥ 5 cycles (28 days of treatment was considered 1 cycle) had a positive impact on the impaired T-cell function in patients with CLL through its modulation of T-cell function. In summary, ibrutinib improved expansion of CD19-directed CAR T cells (CTL019) in association with decreased expression of PD-1 on T cells {Fraietta 2016}.

3.2.2.3. Clinical Data

Evidence showed that T cells collected from subjects exposed to ibrutinib had greater ex vivo expansion and a greater fraction of T cells with a Tcm phenotype compared to T cells from subjects with CLL who were not receiving ibrutinib. The ORR for subjects who had received concurrent ibrutinib was 80%, whereas the ORR for all subjects was only 38% {Geyer 2019}.

In a prospective trial combining a humanized CD19-targeted CAR T cell (CTL119) with ibrutinib, the ORR at 3 months in 14 evaluable subjects was 71% with 6 CRs (43%) {Gill 2018}. At 3 months, 17 of 18 subjects (94%) demonstrated a morphologic CR within the marrow and 15 of 17 subjects were MRD^- by high resolution flow cytometry. Fourteen of 18 subjects were MRD− by IgH sequencing.

In a Phase 1/2 study, it was observed that subjects who received concurrent treatment with ibrutinib (420 mg/day) from at least 2 weeks before leukapheresis until at least 3 months after JCAR014 CAR T-cell infusion had a higher proportion of responders (CR and PR) by International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria in the ibrutinib cohort (14 of 16 evaluable subjects, 88%) compared to the non-ibrutinib cohort (10 of 18 evaluable subjects, 56%) {Gauthier 2018}.

In a Phase 1 clinical trial investigating CD19-targeted CAR T cells incorporating a CD28 costimulatory domain (19-28z), ex vivo expansion of T cells and proportions of $CD4^+/CD8^+$ CAR T cells with a $CD62L^+$ $CD127^+$ immunophenotype were significantly greater in subjects who were receiving ongoing therapy with ibrutinib at leukapheresis {Geyer 2019}. Three of 12 evaluable subjects with CLL receiving conditioning chemotherapy with cyclophosphamide/bendamustine or fludarabine/cyclophosphamide achieved CR (2 had MRD− CR). All subjects achieving CR remained progression-free with a median follow-up of 53 months.

A recent pilot study reported the treatment of 19 subjects with CLL with anti-CD19 CAR T-(4-1BB and $CD3_z$ signaling domains) These patients were treated after ibrutinib failure. {Gauthier 2020}. Patients were heavily pretreated (median number of prior therapies was 5), and 17 subjects (89%) had high-risk cytogenetics (del17p and/or complex karyotype). The minimal time to exposure to ibrutinib was 2 weeks prior to leukapheresis and ibrutinib was

continued for at least 3 months after CAR T-cell infusion. Thirteen subjects (68%) received ibrutinib as planned in the protocol without dose reduction. The ORR by IWCLL criteria assessed at 4 weeks after the infusion was 83%, and 61% achieved MRD^-. The 1-year OS and PFS probabilities were 86% and 59%, respectively. Compared to subjects with CLL who were treated with CAR T cells without ibrutinib, Subjects treated with CAR T cells with concurrent ibrutinib, compared to subjects treated with CAR T cells without ibrutinib, showed was lower severity of cytokine release syndrome (CRS) and lower serum concentrations of CRS-associated cytokines despite equivalent in vivo CAR T-cell expansion.

Other non-randomized studies to prospectively evaluate the combination of ibrutinib and CAR T cells are currently ongoing (NCT03331198, NCT02640209).

In summary, in order to improve the acquired T-cell dysfunction in r/r CLL, prior exposure to ibrutinib, before leukapheresis may lead to improved T-cell fitness and thereby enhance the ability of CAR T cells to expand in vivo and exert antitumor effects.

3.2.3. Rationale for Conditioning Chemotherapy

Increasing levels of conditioning chemotherapy correlates with clinical responses to adoptive cell therapy {Dudley 2008}. Specifically, there appears to be a link between adequate lymphodepletion and adoptively transferred T-cell expansion and function in preclinical models, which demonstrate that the depth and duration of lymphodepletion correlates with anti-tumor activity of the adoptively transferred tumor-specific CD8+ T cells {Gattinoni 2005}. Lymphodepletion may function by eradicating cytokine sinks for the transferred cells, eliminating T regulatory cells, or enhancing antigen-presenting cell activation {Klebanoff 2005}. Cyclophosphamide and fludarabine combination is a potent lymphodepleting regimen. Cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day) are both given for 3 consecutive days. This combination has been studied in subjects with B-cell malignancies and was tolerated by this population {O'Brien 2001} and was also used in the ZUMA-1 trial {Neelapu 2017}.

3.2.4. Rationale for KTE-X19 Dose

The initial dose level of 1 x 10^6 anti-CD19 CAR T cells/kg has been previously shown to be safe and tolerable for subjects with r/r acute lymphocytic leukemia (KTE-C19-103/ZUMA-3) and mantle cell lymphoma (KTE-C19-102/ZUMA-2). The 2 dose levels of KTE--X19 proposed for this study have been previously evaluated in the KTE-C19-103 study, with only 1 DLT at the 2 x 10^6 anti-CD19 CAR T cells/kg dose level; this dose level has also been deemed to be safe and tolerable for subjects with mantle cell lymphoma in KTE-C19-102. KTE-X19 is an autologous anti-CD19 CAR T therapy that is manufactured with the identical CAR construct as axicabtagene ciloleucel, which is approved by the FDA at a dose of 2 x 10^6 anti-CD19 CAR T cells/kg for the treatment of patients with r/r large B cell lymphoma.

3.3. Overall Risk and Benefit Assessment

Kite is developing KTE-X19, an anti-CD19 CAR T-cell product for treatment of patients with r/r B-cell malignancies that express CD19.

While chemoimmunotherapy and targeted therapy represent efficacious treatment options for CLL, the limited depth of response from currently approved targeted agents for CLL underlies the ongoing inability to yield durable responses with finite therapy or to result in a cure for patients with CLL. Also, while allogeneic hematopoietic stem cell transplantation is a potentially curative treatment option for CLL, it is now rarely used as few patients are appropriate candidates due to age and comorbidities.

CAR T-cell therapy offers the possibility of yielding deep MRD− responses and long-term durable responses in CLL without the morbidity and mortality associated with the conditioning treatment or the GVHD of allogeneic transplant. Although the treatment experience to date for CLL has been limited, the early experience shows high rates of response (55 to 90%), with up to 88% MRD^{-}, even in subjects previously treated with ibrutinib {Kochenderfer 2012, Kochenderfer 2015, Porter 2015, Siddiqi 2019, Siddiqi 2018, Turtle 2017}. A subset of subjects remain relapse-free years following a single treatment, evincing a marked depth of response due to anti-CD19 CAR T cells.

KTE-X19 is administered as a single dose following conditioning chemotherapy, and the majority of AEs occur within 30 days of infusion. AEs, which can be severe or even fatal, are well defined, generally reversible, and manageable with no apparent long-term consequences other than B-cell aplasia. The most common events were cytopenias, which are expected from the conditioning chemotherapy, as well as infections, CRS, and neurologic events. Guidelines for management of these AEs are described in the Investigator's Brochure (IB), Section 6.5.

The IB also contains the current understanding of the pathophysiology of CRS/neurotoxicity, and clinical trials experience across KTE-X19 studies to provide context and rationale for management. Furthermore, all sites are trained by the Kite medical monitor on toxicity management including CRS and neurological toxicity at the site initiation visit, and new sites are retrained at first dosing of KTE-X19. Kite provides regular Investigator calls and meetings as well as a toxicity management tool so that sites have quick access to relevant information.

In summary, the rates and durations of high quality clinical responses anticipated within the KTE-X19 study design, the demonstrated safety profile of KTE-X19 to date in other malignant B-cell diseases, and the planned safety monitoring plan (SRT) in this study suggest that the benefits of study participation will outweigh the risks for these subjects with r/r CLL and SLL.

3.4. Participating Sites

Approximately 22 centers located in North America and Europe will participate in this study. During the conduct of the study, additional regions, countries, or sites may be added as necessary.

3.5. Number of Subjects

Participants in this trial will be referred to as "subjects." It is anticipated that up to approximately 27 subjects will be enrolled and dosed in this study.

3.6. Replacement of Subjects

Subjects may continue to be enrolled until the specified approximate number of subjects are dosed with KTE-X19 in Phase 1 for safety evaluation (see Section 10.6).

3.7. Study Duration

3.7.1. Study Duration for Individual Subjects

The duration of the study for individual subjects will vary depending on a subject's screening requirements, response to treatment, survival, and if applicable, timing of transition to the separate LTFU study, KT-US-982-5968 (discussed in Section 3.7.3).

3.7.2. Completion of Study

Completion of the study is defined as the time at which the last subject completes at least 3 months of assessments (the post-treatment follow-up period), is considered lost to follow-up, withdraws consent, or dies. Upon activation of KT-US-982-5968 at subject study site, the subject will be offered the opportunity to complete long-term follow-up assessments under the KT-US-982-5968 protocol.

3.7.3. Long-term Follow-up

All subjects who received an infusion of KTE-X19 will be provided the opportunity to transition to a separate LTFU study, KT-US-982-5968, where they will be monitored for occurrence of late-onset targeted AEs/SAEs suspected to be possibly related to KTE-X19, presence of replication-competent retrovirus (RCR), and/or insertional mutagenesis for up to 15 years from the time of KTE-X19 infusion (also refer to Section 7.13).

In KT-US-982-5968, subjects will continue assessments at timepoints contiguous with the LTFU timepoints in this study.

4. SUBJECT IDENTIFICATION ASSIGNMENT

Each subject who enters the screening period, which starts when the subject signs the informed consent form, will receive a unique subject identification (ID) number. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject. The subject identification number will never be changed even if the subject is rescreened.

5. SUBJECT ELIGIBILITY

5.1. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for enrollment:

101. Documentation of relapsed or refractory CLL and SLL; subjects must have received at least 2 prior lines of treatment, one of which must include a BTK inhibitor

    a. Cohort 1 and 2: Subjects with r/r CLL who have received at least 2 prior lines of treatment, one of which must include a BTK inhibitor

    b. Cohort 3: Subjects with r/r CLL and SLL must present with ≤ 1% circulating tumor cells in peripheral blood or ALC < 5000 cells/µL. Subjects must have received at least 2 prior lines of treatment, one of which must include a BTK inhibitor.

    c. Cohort 4: Subjects with r/r CLL who have received at least 2 prior lines of treatment and must have received ibrutinib as a single agent or in combination with anti-CD20 antibodies, BCL-2 inhibitors, and PI3k inhibitors for at least 6 months as the last line of therapy prior to screening. Ibrutinib administration will continue up to 30 hours prior to leukapheresis. In case of treatment interruption with ibrutinib, the principal investigator should reach out to the medical monitor to discuss.

102. An indication for treatment per IWCLL 2018 criteria {Hallek 2018} and radiographically measurable disease (at least 1 lesion > 1.5 cm in diameter)

103. Adequate hematologic function as indicated by:

    a. Platelet count ≥ 50×10^9/L

    b. Neutrophil count ≥ 0.5×10^9/L

    c. Hemoglobin ≥ 8 g/dL

    Unless lower values are attributable to CLL

104. Adequate renal, hepatic, cardiac and pulmonary function defined as:

    a. Creatinine clearance (as estimated by Cockroft-Gault) ≥ 60 mL/min

    b. Serum ALT/AST ≤ 2.5 x upper limit of normal (ULN)

    c. Total bilirubin ≤ 1.5 mg/dL unless subject has Gilbert's syndrome

    d. Left ventricular ejection fraction (LVEF) ≥ 50%, no evidence of pericardial effusion, no NYHA class III or IV functional classification, no clinically significant arrhythmias

e. No clinically significant pleural effusion

f. Baseline oxygen saturation > 92% on room air

105. Age 18 or older

106. ECOG performance status of 0 or 1

107. Females of childbearing potential must have a negative serum or urine pregnancy test (females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential)

108. At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy or BTKi (ibrutinib or acalabrutinib) at the time the subject is planned for leukapheresis, except for systemic inhibitory/stimulatory immune checkpoint therapy. At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy at the time the subject is planned for leukapheresis (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists)

5.2. Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not eligible for enrollment:

201. A history of treatment including any of the following:

a. Prior CD19 directed therapy

b. Treatment with alemtuzumab within 6 months before enrollment

c. Allogeneic hematopoietic stem cell transplant (SCT) or donor lymphocyte infusion (DLI) within 6 months prior to enrollment

d. Live vaccine administration within 4 weeks before enrollment

e. Systemic immunosuppression or systemic treatment for any autoimmune disease not related to CLL in the 2 years before enrollment

202. Acute GVHD grade II-IV by Glucksberg criteria or severity B-D by IBMTR index

203. History of autoimmune disease resulting in end-organ injury unless attributable to CLL (eg, ITP, AIHA)

204. Diagnosis of Richter's transformation or a history of malignancy. Exceptions include:

a. Non-melanoma skin cancer or carcinoma in situ (eg, skin, cervix, bladder, breast)

b. Superficial bladder cancer

c. Asymptomatic localized low grade prostate cancer for which watch-and-wait approach is standard of care

d. Any other cancer that has been in remission for > 3 years prior to enrollment

205. History of severe hypersensitivity reaction attributed to aminoglycosides or any of the agents required for treatment in this study

206. CNS disease including:

a. Known presence of involvement by CLL/SLL

b. History of any CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, any autoimmune disease with CNS involvement, posterior reversible encephalopathy syndrome (PRES), or cerebral edema with confirmed structural defects (eg, by whole-neuroaxis magnetic resonance imaging [MRI])

Note: Subjects with a history of seizures requiring antiseizure therapy are excluded.

207. History of concomitant genetic syndrome associated with bone marrow failure such as Fanconi anemia, Kostmann syndrome, Shwachman-Diamond syndrome

208. History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months before enrollment

209. History of symptomatic deep vein thrombosis or pulmonary embolism requiring systemic anticoagulation within 6 months before enrollment. Subjects taking prophylactic anticoagulation are eligible.

210. Primary immunodeficiency

211. History of human immunodeficiency virus (HIV) infection or acute or chronic active hepatitis B or C infection. Subjects with history of hepatitis infection must have cleared their infection as determined by standard serological and genetic testing per current Infectious Disease Society of America (IDSA) guidelines or applicable country guidelines.

212. Presence of active fungal, bacterial, viral infection or any infection requiring antimicrobial treatment for management. Simple UTI and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the Kite medical monitor

213. Presence of any indwelling line or drain (eg, percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, pleural/peritoneal/pericardial catheter). Ommaya reservoirs and dedicated central venous access catheters such as Port-a-Cath or Hickman catheters are permitted

214. Women of childbearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential.

215. Subjects of childbearing potential who are not willing to practice birth control from the time of consent through 6 months after the administration of conditioning chemotherapy or KTE-X19, whichever is longer.

216. In the investigator's judgment, subject is unlikely to complete all protocol-required study visits or procedures including follow-up visits or comply with requirements for participation

217. Any medical condition likely to interfere with assessment of safety or efficacy of study treatment

6. PROTOCOL TREATMENT

6.1. Study Treatment

6.1.1. Leukapheresis

Leukapheresis refers to the procedure for collecting PBMCs that are used to manufacture the subject-specific KTE-X19.

Subjects will undergo leukapheresis to obtain T cells for the manufacturing of KTE-X19. Leukapheresed cells obtained at participating centers will be shipped to the sponsor's manufacturing facility as described in the Investigational Product Manual (IPM).

6.1.2. Bridging Therapy (Optional)

At the discretion of the investigator, bridging therapy may be considered for all subjects, particularly those with rapidly progressive disease at screening.

Bridging therapy may consist of:

- Continuation of the immediately preceding line of treatment with targeted agent(s) (eg, BTK inhibitors, BCL-2 inhibitors, or PI-3K inhibitors) at the discretion of the principal investigator

- Anti-CD20 antibody therapy and/or high dose corticosteroids. Dexamethasone 40 mg or its equivalent is recommended though the choice, dose and route of administration of corticosteroid can be adjusted for age and comorbidities per local and institutional guidelines. Corticosteroids at a dose of ≥ 5 mg prednisone (or equivalent) must be avoided for 7 days prior to leukapheresis and 5 days prior to KTE-X19 administration.

Bridging therapy may be administered after leukapheresis and must be discontinued 48 hours prior to administration of conditioning chemotherapy. If subjects receive bridging therapy, they must be restaged with laboratory testing, imaging (computed tomography [CT] or MRI scan of the head, neck, chest, abdomen and pelvis), and bone marrow evaluation after the completion of the bridging therapy and prior to administration of conditioning chemotherapy.

6.1.3. Conditioning Chemotherapy

Conditioning chemotherapy refers to fludarabine and cyclophosphamide used for lymphodepletion prior to administration of KTE-X19.

Conditioning chemotherapy will be supplied by the investigative site unless otherwise noted.

Refer to the current product label for guidance on packaging, storage, preparation, administration, and toxicity management associated with the administration of chemotherapy agents.

The investigational medicinal product (KTE-X19) must be available before initiation of conditioning chemotherapy.

6.1.3.1. Fludarabine

Fludarabine phosphate (hereafter, fludarabine) is a synthetic purine nucleoside that differs from physiologic nucleosides in that the sugar moiety is arabinose instead of ribose or deoxyribose. Fludarabine is a purine antagonist antimetabolite.

Refer to the most recent version of the package insert for specific details surrounding the administration of fludarabine.

6.1.3.2. Cyclophosphamide

Cyclophosphamide is a nitrogen mustard-derivative that acts as an alkylating agent following conversion to active metabolites in the liver and has potent immunosuppressive activity. The serum half-life after intravenous (IV) administration ranges from 3 to 12 hours; the drug and/or its metabolites can be detected in the serum for up to 72 hours after administration.

Refer to the most recent version of the package insert for specific details surrounding the administration of cyclophosphamide.

6.1.3.3. Mesna

Mesna is a detoxifying agent used to inhibit the hemorrhagic cystitis induced by chemotherapy. The active ingredient in mesna is a synthetic sulfhydryl compound designated as sodium-2-mercaptoethane sulfonate with a molecular formula of $C_2H_5NaO_3S_2$.

Mesna should be administered per institutional guidelines. Refer to the most recent version of the package insert for specific details surrounding the administration of mesna.

6.1.4. KTE-X19

KTE-X19 is the IP for this study.

KTE-X19 is supplied cryopreserved in cryostorage bags. The product in the bag is slightly cloudy and cream to yellow color. The cryostorage bag containing KTE-X19 arrives frozen in a liquid nitrogen dry shipper. The bag must be stored in vapor phase of liquid nitrogen and remain frozen until the subject is ready for treatment to assure that viable live autologous cells are administered to the subject. Several inactive ingredients are added to the product to assure viability and stability of the live cells through the freezing, thawing, and infusion process.

KTE-X19 is a subject-specific product. The product is labelled per local regulations with the subject's unique subject ID number assigned at the time of screening. Upon receipt, verification that the product and subject-specific labels match the subject's information (eg, subject ID number) is essential. Do not infuse the product if the information on the subject-specific label does not match the intended subject. The volume of KTE-X19 infused, the thaw start/stop time, and KTE-X19 administration start/stop time, will all be noted in the subject medical record.

The product must not be thawed until the subject is ready for the infusion. Refer to the IPM for details and instruction on storage, thawing, and administration of KTE-X19.

There have been no instances of accidental overdose of subjects in this program to date. In case of accidental overdose, treatment should be supportive. Corticosteroid therapy may be considered if any dose is associated with severe toxicity.

If any problems related to the use of KTE-X19 or any products that support the management of KTE-X19 (eg, cryostorage bags, subject ID labels) are identified, research staff should report the problem per the instructions in the IPM.

6.2. Concomitant Therapy

Concomitant therapy refers to treatment that subjects receive during the conduct of the study.

Investigators may prescribe any concomitant therapies deemed necessary to provide adequate supportive care except those medications listed in Section 6.3.

The investigator is responsible for reporting all concomitant medications as follows:

Table 1. Reporting Requirements for Concomitant Medications

Subjects who screen-fail	Subjects who are enrolled, but do not receive KTE-X19 infusion	Subjects who are enrolled and receive KTE-X19 infusion
Concomitant therapies related to serious adverse event(s) will be recorded.	Concomitant therapies will be recorded from the date of the informed consent until 30 days after the last study-specific procedure has occurred (eg, leukapheresis, conditioning chemotherapy) or until the initiation of new anticancer therapy, whichever occurs first.	• Concomitant therapies including medications, intubation, dialysis, oxygen, and blood products will be recorded from the date of the informed consent until 3 months after completing treatment with KTE-X19. • After this 3-month follow-up period, targeted concomitant therapies will be recorded for either 24 months after KTE-X19 infusion or until disease progression, whichever occurs first. o Targeted concomitant therapies include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations.

Specific concomitant therapy collection requirements and instructions are included in the case report form (CRF) completion guidelines.

6.3. Excluded Medications

Excluded medications refer to treatment that is not to be administered, unless otherwise specified, during the conduct of the study.

Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis and 5 days prior to KTE-X19 administration.

Systemic corticosteroids may not be administered as premedication to subjects for whom CT scans with contrast are contraindicated (ie, subjects with contrast allergy or impaired renal clearance). Such subjects should undergo non-contrast CT scans instead.

Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after KTE-X19 administration unless used to manage severe KTE-X19-related toxicities. Other medications that might interfere with the evaluation of KTE-X19, such as nonsteroidal anti-inflammatory agents, should also be avoided for the same period unless medically necessary.

Therapeutic doses of systemic anticoagulants, such as unfractionated heparin and low-molecular weight heparin, should be avoided anytime subjects are at risk of bleeding due to thrombocytopenia when possible.

Non-study treatment for CLL/SLL is prohibited prior to disease progression on study.

If permissibility of a specific medication/treatment is in question, contact the Kite medical monitor.

6.4. Subsequent Therapy

Subsequent therapy refers to treatment administered after KTE-X19 that is necessary to treat a CLL/SLL.

Subsequent therapy such as non-study specified chemotherapy, immunotherapy, targeted agents, SCT, or radiation therapy, will be recorded for all enrolled subjects until one of the following happens: the subject transitions to the KT-US-982-5968 LTFU study, is considered lost to follow-up, withdraws consent, or dies.

For subjects who are enrolled, but do not receive KTE-X19 infusion, any additional anticancer therapy will also be collected until the subject completes the participation in the current study, is considered lost to follow up, withdraws consent, or dies.

7. STUDY PROCEDURES

Research staff should refer to the SOA Table 3 and Table 4 for an outline of the procedures required. Additional information related to a few study assessments/procedures is further described below.

The visit schedule is calculated from KTE-X19 infusion on Day 0.

Refer to the CRF completion guidelines for data collection requirements and best practices for documentation of study procedures.

7.1. Informed Consent

Before a subject participates in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequately explaining the study design, anticipated benefits, and potential risks. Subjects should sign the most current Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved informed consent form (ICF) before any study-specific activity or procedure is performed.

The consent process and the subject's agreement or refusal to participate in the study must be documented in the subject's medical records. If the subject agrees to participate, the ICF must be signed and dated by both the subject and the person who conducted the informed consent discussion. The original signed ICF will be retained in accordance with institution policy and IRB/IEC requirements, and a copy of the ICF will be provided to the subject.

All subjects who are enrolled into the study should be re-consented with any updated version of the IRB/IEC-approved ICF if the new version is relevant to their participation.

7.2. Screening

Investigative sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected in the screening log should include limited information, such as the date of screening, date the subject was enrolled, or the reason for why the subject failed screening.

The screening period begins on the date the subject signs the IRB/IEC-approved ICF and continues through confirmation of eligibility into the study. Informed consent must be obtained before completion of any non-SOC study-specific procedures. Procedures that are part of SOC are not considered study-specific and, therefore, may be performed prior to obtaining consent and used to confirm eligibility provided they occur within the time allowance outlined below and in the SOA.

After written informed consent has been obtained, Kite Pharma, Inc., will assign a screening number to the subject, as described in Section 7.1.

See Section 7.2.1 for the study procedures for subjects who rescreen into the study.

Only subjects who meet the eligibility criteria listed in Section 5 will be enrolled into the study. If at any time prior to enrollment the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure.

Refer to the SOA for a listing of study procedures to be completed during the screening period.

7.2.1. Rescreening

Subjects who do not meet the eligibility criteria during the 28-day screening period will be permitted to rescreen one time. Subjects will retain the same subject ID number assigned at the original screening. If rescreening occurs within 28 days of the signing of the original informed consent, it is only necessary to perform the procedure(s)/assessment(s) that did not originally meet the eligibility criteria; all other initial screening procedures/assessments do not need to be repeated. If rescreening occurs, or leukapheresis is delayed more than 28 days from the signing of the original informed consent, subjects must be re-consented and repeat all screening procedures/assessments.

7.3. Demographic Data

Demographic data will be collected as per country and local regulations and guidelines. Where applicable, demographic data will include sex, year of birth, race, ethnicity, and country of enrollment to study a possible association between these variables and subject safety and treatment effectiveness.

7.4. Medical and Treatment History

Relevant medical history prior to the start of AE reporting (see Section 9.2) will be collected. Relevant medical history is defined as data on the subject's current medical condition that would be typically shared in a referral letter. In addition to the medical history, all history related to the subject's disease, treatment, and response to treatment will be collected and must date back to the original diagnosis. All findings will be recorded in the CRFs.

For subjects who are being referred from another clinic or institution to the participating research center, copies from the subject's chart should be obtained.

7.5. Physical Exam, Vital Signs, and Performance Status

Physical exams will be performed during screening and at times noted in the SOA. All physical exam changes noted in subsequent exams when compared to the baseline exam will be reported as AEs per Section 9.1. Subjects with new-onset symptoms related to CRS should undergo physical exam at least daily until symptoms resolve to baseline.

Vital signs, including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature, will be monitored and recorded at screening and at times outlined in the SOA. In addition to the time points outlined in the SOA, it is recommended that vital signs are monitored during and after the KTE-X19 infusion and as clinically indicated.

Performance status as measured by the ECOG scale will be performed to quantify the subject's general well-being and ability to perform activities of daily life.

7.6. Cardiac Function

Each subject's cardiac function, as measured by LVEF, will be assessed during the screening period to confirm study eligibility. No evidence of pericardial effusion will also be confirmed, per study eligibility criteria. LVEF may be assessed by echocardiogram (ECHO) or MUGA, and pericardial effusion may be assessed by ECHO or CT/MRI. Imaging that was performed after the subject's last chemotherapy treatment may also be used to confirm eligibility, provided that it occurred ≤ 28 days prior to signing the consent.

To establish a baseline, a 12-lead electrocardiogram (ECG) will also be performed during the screening period.

7.7. Neurological Examination

Subjects neurological status should be evaluated at screening to establish a baseline. After enrollment, subjects should be evaluated for any neurological symptoms at each of the timepoints specified in the SOA. During the hospitalization period, evaluations of neurological status may need to be increased. Changes in neurological status (level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, and neuropsychological findings (eg, speech, cognition and emotion)) should be reported as an AE per Section 9.

For new onset of neurologic symptoms (eg, severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurologic findings on physical exam), neurologic assessment should be performed at least daily until symptoms resolve to baseline. In addition, brain imaging should be considered.

Subjects with new onset Grade ≥ 2 neurologic symptoms post-KTE-X19 infusion will have a lumbar puncture (LP) performed to evaluate for potential causes. A portion of the cerebrospinal fluid (CSF) will be submitted to the central lab for evaluation of KTE-X19 levels and cytokines.

7.8. Disease Assessment

Binet and Rai staging will be assessed at screening (Appendix 1). Subjects will be evaluated for disease response by the site investigator at times indicated in the SOA. Disease response assessments will be per IWCLL 2018 criteria {Hallek 2018}, (Appendix 3). Laboratory samples to assess disease response will be collected and evaluated per the SOA and are outlined in Section 7.14.

7.8.1. Radiology Assessment

Diagnostic quality contrast-enhanced (unless contraindicated) CT (preferred) or MRI of the head, neck, chest, abdomen and pelvis must be performed within 28 days before enrollment to confirm eligibility. Scans obtained as part of SOC before signing of the ICF and within 56 days before enrollment can be used for eligibility.

If the subject received treatment for CLL/ SLL after the eligibility images were obtained, then additional baseline images must be taken after the completion of CLL/SLL treatment and within 28 days before conditioning chemotherapy. For subjects receiving bridging therapy, baseline images must be taken either after bridging therapy is completed or within 48 hours prior to the administration of conditioning chemotherapy.

The same imaging modality should be used when possible for post-treatment response assessments as outlined in the SOA and in the event of suspected disease progression. See Section 7.7 for imaging requirements for neurological symptoms.

7.8.2. Bone Marrow Assessment

A bone marrow aspirate and biopsy is required per the SOA at the following timepoints:

- Screening or prior to conditioning chemotherapy (if applicable)
  - Subjects receiving bridging therapy must have a bone marrow aspirate and biopsy performed after bridging therapy is completed or within 48 hours prior to administration of conditioning chemotherapy; the screening bone marrow aspirate and biopsy may be deferred until this time for subjects receiving bridging therapy.
- Day 28
- Month 6
  - The Month 6 bone marrow evaluation is not required if the subject is confirmed to be MRD- per bone marrow evaluation prior to Month 6.
- Subsequent to any evaluation following Day 28 when the subject's hematologic and radiographic response becomes consistent with CR/CRi with peripheral blood MRD- in order to establish a CR/CRi with bone marrow MRD- per IWCLL 2008 criteria (see Appendix 3).

In addition, a bone marrow evaluation (biopsy and/or aspirate) should be performed at the following timepoints:

- For persistent cytopenias and to diagnose hemophagocytic lymphohistiocytosis (HLH) if appropriate. Refer to the IB for additional information.
- At the time of progressive disease.

For subjects who consent to the optional nodal biopsy, the biopsy may be collected at the following timepoints:

- Screening
- Anytime during Day 7 though 14

- At the time of progressive disease

Whenever obtained, a portion of the bone marrow aspirate and biopsy specimen must be sent to the central laboratory for analysis.

7.9. Cell Collection and Study Treatment Schedule and Administration

7.9.1. Leukapheresis

7.9.1.1. Requirements for Initiating Leukapheresis

Before leukapheresis commences, the following criteria must be met:

- Subjects must remain eligible per the eligibility criteria outlined in Section 5 prior to the start of leukapheresis.
- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of leukapheresis and results are outside the eligibility criteria listed in Section 5, contact Kite's medical monitor prior to proceeding with leukapheresis.
- No evidence or suspicion of an infection
- Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis
- If criteria are not met, leukapheresis must be delayed until the event resolves. If leukapheresis is delayed more than 5 days after eligibility confirmation, baseline complete blood count (CBC) with differential and chemistry panel must be repeated. If results are outside the eligibility criteria listed in Section 5, contact the medical monitor prior to proceeding with leukapheresis.

The leukapheresis visit should occur within approximately 5 days of eligibility confirmation. After a subject commences leukapheresis, the subject will be considered enrolled into the study.

After the above criteria are met, mononuclear cells will be obtained by leukapheresis (12 to 15 L) apheresis with a goal to target approximately 5 to 10 x 10^9 mononuclear cells. The leukapheresed cells are then packaged for expedited shipment to the manufacturing facility as described in the IPM.

Refer to the SOA Table 3 for a listing of study procedures to be completed on the leukapheresis collection day.

7.9.2. Bridging Therapy (Optional)

Refer to the SOA Table 3 for a listing of study procedures to be completed at the time of bridging therapy.

7.9.3. Conditioning Chemotherapy and KTE-X19 Infusion

Administration of CAR T cells to subjects with ongoing infection or inflammation, even if such processes are asymptomatic, increases the risk of high grade and fatal toxicity. All efforts should be made to rule out such conditions prior to cell infusion. Signs, symptoms, or abnormal laboratory results attributed to the malignancy (eg, "tumor fever," elevated C-reactive protein [CRP]) are diagnoses of exclusion that require a documented workup to establish. Conditioning chemotherapy and KTE-X19 infusion should be initiated only once it is reasonably assured that cell infusion can safely proceed.

Refer to Section 7.9.4 for Requirements to Work-up Potential Infectious and/or Inflammatory States.

7.9.3.1. Conditioning Chemotherapy Period

7.9.3.1.1. Requirements for Initiating Conditioning Chemotherapy

If any of the following criteria are met prior to the initiation of conditioning chemotherapy, then the work-up listed in Section 7.9.4 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38 degrees Celsius within 72 hours of conditioning chemotherapy
- CRP > 100 mg/L anytime between enrollment to start of conditioning chemotherapy
- White blood cell (WBC) count or WBC differential concerning for infectious process between enrollment to start of conditioning chemotherapy (eg, WBC > 20,000, rapidly increasing WBC, or differential with high percentage of segs/bands)

Additionally:

- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of conditioning chemotherapy and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with conditioning chemotherapy.
- Complete history and physical exam including head, ears, eyes, nose, and throat (HEENT), cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.
- The subject must not have received systemic antimicrobials for the treatment of a known or suspected infection within 48 hours before conditioning chemotherapy (prophylactic use of antimicrobials is allowed).
- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.

- If a subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determined by the investigator in consultation with infectious disease service (if applicable)

- Most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (eg, bacterial, viral serologies, PCR, stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for cultures to become positive.

Once the above criteria are met, then the subject can proceed with conditioning chemotherapy.

7.9.3.1.2. Conditioning Chemotherapy Administration (Day –5 Through Day –3 Prior to KTE-X19 Infusion)

Subjects will receive a conditioning chemotherapy regimen consisting of cyclophosphamide and fludarabine. The first dose of conditioning chemotherapy will be designated as Day –5. Subjects will initiate conditioning chemotherapy with cyclophosphamide and fludarabine beginning on Day –5 and through Day –3, with 2 rest days (Day –2 and Day –1) before receiving KTE-X19. The 3-day conditioning chemotherapy regimen will be administered in an outpatient setting.

Before conditioning chemotherapy commences, the criteria outlined in Section 7.9.3.1.1 must be met.

Provided the criteria for conditioning chemotherapy are met, the 3-day conditioning regimen of fludarabine and cyclophosphamide will be administered in accordance with the following daily dosing instructions.

- IV hydration with a balanced crystalloid according to institutional guidelines prior to administration of cyclophosphamide on the day of infusion

- Cyclophosphamide 500mg/m^2/day IV over approximately 30-60 minutes

- Fludarabine 30mg/m^2/day IV over approximately 30 minutes

- Additional IV hydration with a balanced crystalloid according to institutional guidelines to be administered upon completion of the cyclophosphamide infusion

- Mesna to be administered per institutional guidelines

Subjects should be instructed to drink plenty of liquids during chemotherapy and throughout the 24-hour period following chemotherapy (approximately 2 L/24 hours). In general, subjects should be kept well-hydrated but closely monitored to prevent fluid overload.

Refer to the SOA Table 3 for a listing of study procedures to be completed during the KTE-X19 conditioning chemotherapy period.

7.9.3.2. KTE-X19 Treatment Period

7.9.3.2.1. Requirements for Initiating KTE-X19 Infusion

If any of the following criteria are met prior to the initiation of KTE-X19 infusion, then the work-up listed in Section 7.9.4 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38 degrees Celsius within 72 hours of KTE-X19 infusion
- CRP > 100 mg/L anytime between enrollment to start of KTE-X19 infusion
- WBC count or WBC differential concerning for infectious process between enrollment to start of KTE-X19 infusion (eg, WBC > 20,000, rapidly increasing WBC, or differential with high percentage of segs/bands)

Additionally:

- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of KTE-X19 infusion and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with KTE-X19 infusion (except for peripheral blood cell counts that have been impacted by conditioning chemotherapy).
- Complete history and physical exam including HEENT, cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.
- The subject must not have received systemic antimicrobials for the treatment of a known or suspected infection within 48 hours before KTE-X19 (prophylactic use of antimicrobials is allowed).
- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.
- If a subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determined by the investigator in consultation with infectious disease service (if applicable)
- Most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (eg, bacterial, viral serologies, PCR, stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for cultures to become positive.

Once the above criteria are met, then the subject can proceed with administration of KTE-X19.

If the KTE-X19 infusion is delayed > 2 weeks, protocol guidelines should be followed regarding the need for repeat conditioning chemotherapy.

7.9.3.2.2. Hospitalization for KTE-X19 Infusion

Subjects will be hospitalized to receive KTE-X19 infusion and will remain in the hospital for at least 7 days to monitor for signs and symptoms of CRS and neurologic events. Post infusion monitoring of patients must be for a minimum of 7 days unless otherwise required by country regulatory agencies. Refer to Appendix 4.

Subjects should not be discharged from the hospital until all KTE-X19-related non-hematological toxicities resolve to ≤ Grade 1 or return to baseline. Subjects may be discharged with non-critical and clinically stable or improving toxicities (eg, renal insufficiency) even if > Grade 1, if deemed appropriate by the investigator. Subjects should remain in a hospital for ongoing KTE-X19-related fever, hypotension, hypoxia, or ongoing neurologic events > Grade 1, or if deemed necessary by the investigator.

Subjects should be instructed to remain within proximity of the clinical study site for at least 4 weeks following KTE-X19 infusion. Subjects should be advised to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks following KTE-X19 infusion. Subjects and their family members/caregivers should be educated on potential CRS and neurologic symptoms, such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. Subjects or their family members/caregivers should be instructed to immediately contact the treating investigator or seek immediate medical attention if any of these symptoms develop.

7.9.3.2.3. KTE-X19 Premedication Dosing

The following pre KTE-X19 infusion medications should be administered approximately 1 hour prior to infusion. Alternatives to the recommendations below should be discussed with the medical monitor.

- Acetaminophen 650 mg PO or equivalent
- Diphenhydramine 12.5 mg administered either orally or via IV or equivalent

7.9.3.2.4. KTE-X19 Administration Day 0

KTE-X19 will be administered at one of the dose levels as outlined in Section 3.1.

Refer to the SOA for a listing of study procedures to be completed during the KTE-X19 treatment period.

Central venous access, such as a port or a peripherally inserted central catheter, is required for the administration of KTE-X19. Catheter care, per institutional guidelines, should be followed. Materials and instructions for the thawing, timing, and administering of KTE-X19 are outlined in

the IPM. Vital signs should be measured during and after KTE-X19 treatment (See Section 7.5). The IPM must be reviewed prior to administration of KTE-X19.

Research sites should follow institutional guidelines for the infusion of cell products.

7.9.4. Requirements to Work-up Potential Infectious and/or Inflammatory States

In the absence of an identified source of infection (eg, line infection, pneumonia on chest x-ray), the minimum workup to be performed prior to administration of conditioning chemotherapy and/or KTE-X19 consists of:

- Call Kite medical monitor
- Infectious disease service consult (if applicable)
- CT imaging of the chest, abdomen, and pelvis with IV contrast. If there is a medical contraindication to contrast, then non-contrast CT is allowed.
- The following must be performed (prior to the initiation of antimicrobials if clinically feasible):
  - Blood cultures (aerobic and anaerobic x2 bottles each, cultured for 48 hours) and urinalysis and urine culture. Deep/induced sputum culture if clinically indicated.
  - All indwelling lines such as central venous catheters should be examined for any signs of infection and additional cultures should be drawn from the line
  - Nasopharyngeal-throat swab or equivalent assay for viral infection such as influenza A/B (including H1N1), parainfluenza 1/2/3, adenovirus, respiratory syncytial virus, coronavirus, metapneumovirus
  - Collection of fungal cultures and markers as appropriate (eg, galactomannan, fungitell)
  - Collection of appropriate serum viral studies (eg, cytomegalovirus)
- If a CNS process is suspected, appropriate brain imaging and subsequent LP with cytology, culture, Gram stain, and viral PCR should be performed
- Any additional sign or symptom-directed investigation should be performed as clinically indicated

Prior to proceeding with conditioning chemotherapy and/or KTE-X19 infusion, the above workup must not suggest the presence of an active infection and all requirements for conditioning chemotherapy and/or KTE-X19 infusion must be satisfied. If the KTE-X19 infusion is delayed > 2 weeks following conditioning chemotherapy, protocol guidelines should be followed regarding the need for repeat conditioning chemotherapy.

If the above workup was triggered due to CRP > 100mg/L, CRP should be repeated and if CRP continues to increase significantly evaluation should be performed for any other potential infectious or inflammatory condition not previously evaluated.

7.10. Toxicity Management

To date, the following important risks have been identified with KTE-X19: CRS, neurologic toxicities, infections, hypogammaglobulinemia, and cytopenias. Refer to the current KTE-X19 IB for details regarding these events and management guidance for potential risks associated with KTE-X19. Refer to the SOA (Table 3 and Table 4) for the timing of evaluations for CRS and neurological related symptoms.

As the safety experience with KTE-X19 increases, the management guidance may be updated. Therefore, it is important to always refer to the most current version of the KTE-X19 IB for guidance regarding managing KTE-X19 related toxicities. Additional information and management recommendations can also be found in the IB regarding possible complications associated with malignancy and cancer treatment.

7.11. Laboratory

7.11.1. Local Lab Analysis

Assessments listed in Table 2 will be performed at the local laboratory at the time points indicated in the SOA.

Table 2. Clinical Laboratory Parameters

Serum Chemistries	Hematology	Other
Albumin	CBC with differential[b]	CRP
ALT/GPT		Ferritin
ALP		Pregnancy test
AST/GOP		Viral testing[c]
Bicarbonate total		
Bilirubin total[a]		
BUN or urea[a]		
Calcium total		
Chloride		
Creatinine		
Glucose		
LDH		
Magnesium total		
Phosphorus		
Potassium		
Sodium		
Uric acid[b]		

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; CRP, C-reactive protein; GOP, serum glutamic-oxaloacetic transaminase; GPT, serum glutamic-pyruvic transaminase; LDH, lactate dehydrogenase.

a If BUN test cannot be analyzed by the local lab, urea should be analyzed. If total bilirubin is elevated, then direct bilirubin should be obtained.
b Per institutional guidelines but must include WBC, neutrophils or ANC, lymphocytes or ALC, hemoglobin, platelets.
c In European Union (EU) sites, viral serologic tests (eg, HIV, Hep B, Hep C) will be carried out per institution guidelines and EU regulations, unless otherwise required by country regulatory agencies (refer to Appendix 4 for details), to evaluate for active infection (see SOA)

7.11.2. Central Laboratory Analyses

The following biospecimens will be sent to the central laboratory(ies) for sample processing, accessioning, and distribution to specialty laboratories or Kite:

- Bone marrow biopsy and aspirate, nodal biopsy and/or peripheral blood sample for CLL/SLL immunophenotyping, confirmation of diagnosis and genetic analyses related to CLL/SLL prognostic factors
- Peripheral blood for PK (levels of anti-CD19 CAR T cells), replication-competent retrovirus (RCR) testing, and assessment of B-cell aplasia and immune reconstitution
- Serum for pharmacodynamics (cytokine levels) and immunogenicity testing (development of antibodies against KTE-X19)
- CSF or other bodily fluids to monitor for the presence of anti-CD19 CAR T cells, other immune cell subsets and for the purpose of understanding the mechanism of action and safety profile of KTE-X19

Samples are obtained at the times indicated in the SOA. Complete instructions regarding sample processing and submission to central laboratory(ies) are provided in the Central Laboratory Manual.

All samples, as well as any derivatives from these samples, may be stored up to 15 years from the last subject dosed to address exploratory scientific questions related to the treatment or disease under study. Each subject will have the right to have the sample material destroyed at any time by contacting the investigator who, in turn, can contact the sponsor. The investigator should provide the sponsor with the study and subject number so that the sample can be located and destroyed. For subjects who withdraw consent, any samples that were not requested to be returned or destroyed will remain with the sponsor, and any data that may be generated from these samples will be entered in the study database.

Multiple specialty laboratories may be employed for specific analyses, such as baseline/archival tumor assessments, confirmation of diagnosis, PK, pharmacodynamics, and special safety analyses (immunogenicity and RCR testing). Refer to the Central Laboratory Manual for instructions regarding submitting such samples to the appropriate laboratory.

Central lab immunophenotyping of peripheral blood obtained at screening will confirm the diagnosis of CLL/SLL.

7.11.2.1. Exploratory Analyses of Tumor Characteristics

Tumor samples will be retained for possible exploratory analyses, such as the following:

- Cancer gene mutations and cancer gene expression profiling
- Cytogenetic analysis specific to disease indication
- Other exploratory analysis related to the tumor immune microenvironment

In the event of disease progression, sites are encouraged to submit CLL/SLL samples (eg, blood, nodal biopsy, bone marrow) to the central laboratory for exploratory biomarker analysis, which may include CD19 expression, gene expression profiling, and analysis of tumor-specific DNA alterations.

Complete details concerning these analyses will be provided in separate documents regarding bioanalytical analyses.

7.11.2.2. Pharmacokinetics and Pharmacodynamics

PK and pharmacodynamic analysis will be performed on blood (levels of anti-CD19 CAR T cells) or serum (cytokines) at the intervals outlined in the SOA to evaluate predictive markers for the efficacy and safety of KTE-X19. The following cytokines and chemokines may be included in the panel: homeostatic, pro-inflammatory and immune modulating cytokines IL-2, IL-6, IL-10, IL-12p40/p70, IL-15, IL-17a, tumor necrosis factor (TNF)-α, interferon (IFN)-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF); acute phase reactants, such as CRP; chemokines IL-8, monocyte chemoattractant protein (MCP)-1 and macrophage inflammatory protein (MIP)-1α and interferon-inducible protein (IP)-10; and HLH related markers ferritin and IL-2Rα.

CSF draws and additional subject samples (eg, pleural fluid) will be obtained from subjects who develop Grade ≥ 2 neurologic events for evaluation of inflammatory cytokine and chemokine levels and presence of anti-CD19 CAR T cells. As applicable, lymphocyte populations residing in the CSF, or other subject samples, may also be monitored for the purpose of understanding the safety profile of KTE-X19.

7.11.2.3. Product Characteristics

Samples of apheresis material or final product will be retained and tested by the sponsor or specialty laboratory for the purpose of understanding the mechanism of action and safety profile of KTE-X19.

7.11.2.4. Immunogenicity

Immunogenicity will be evaluated utilizing a screening enzyme-linked immunosorbent assay (ELISA) designed to detect antibodies present in serum that react against the murine monoclonal antibody FMC63, the parent antibody from which the scFv utilized in the KTE-X19 product is derived.

Blood draws for determination of the presence of anti-FMC63 antibodies using the screening assay will be performed at intervals outlined in the SOA or as clinically indicated.

In the event of a positive result, a qualified confirmatory assay will be utilized to validate positive results observed in the screening assay. Analysis of PK profiles and clinical outcomes in

subjects with a positive screening or confirmatory result at baseline or after treatment with KTE-X19 will also be conducted to determine the impact of anti-FMC63 antibodies on the efficacy and safety of KTE-X19 therapy.

Immunogenicity will also be addressed by a manual review of AE terms indicative of infusion-related events and anaphylactic reactions among subjects who test positive for these antibodies.

7.11.2.5. RCR Testing

KTE-X19 comprises T cells transduced with a γ-retroviral vector; hence, there is a theoretical risk for RCR developing in exposed subjects. Additional information is provided in the IB.

RCR testing will occur at baseline, Month 3, Month 6, and Month 12. Thereafter, samples will be collected yearly and held for up to 15 years. If a subject tests positive for RCR at any time point within the first year, samples will continue to be collected and tested yearly for up to 15 years or as clinically indicated. Samples for RCR testing are collected as part of the blood draw for PBMCs as noted in the SOA.

7.12. Post-treatment Assessment Period

After completing KTE-X19 infusion, all subjects will return to the clinic for post-treatment follow-up visits and complete the study procedures and assessments per the SOA.

If a subject progresses before completion of the Month 3 visit, then the following procedures will be completed:

- Labs (if not already collected at visit in which progressive disease/relapse was confirmed):
  - Blood draw for PBMC
  - A PBMC sample should be collected at time of progression and prior to starting subsequent anticancer therapy
  - Anti-KTE-X19 antibodies
  - β-HCG pregnancy test (serum or urine) on all women of childbearing potential
- Proceed to the long-term follow-up period (see Section 7.14 and the SOA for details).

Following the initial hospitalization for the KTE-X19 infusion, if the subject is hospitalized with any KTE-X19 related AE, the following labs will be collected:

- PBMCs on day of admission, then weekly, and on day of discharge
- Cytokine levels on day of admission, then weekly, and on day of discharge

7.13. Long-term Follow-up Period

All enrolled subjects will be followed in the long-term follow-up period for safety, survival and disease status, if applicable, for up to 15 years. Subjects will begin the long-term follow-up period after they complete the post-treatment assessment period. Refer to the SOA for a listing of study procedures and disease assessments to be completed during the long-term follow-up period.

After completion of at least 3 months of assessments in the KTE-C19-108 study (refer to Section 3.7.2), all subjects who received an infusion of KTE-X19 will be given the opportunity to transition to a separate LTFU study, KT-US-982-5968. Upon activation of KT-US-982-5968 at each study site, subjects will be asked to provide informed consent and complete the remaining time of their LTFU period.

Subjects who receive infusion of KTE-X19, but who experience disease progression, will be followed in the long term follow up period and undergo the following assessments at the timepoints outlined in the SOA:

- Survival status
- Serious adverse event (SAE) reporting (see Section 9)
- Concomitant medications documentation (see Section 6.2)
- Subsequent therapy for CLL/SLL (see Section 6.4)
- Blood draw for:
  - PBMCs
  - If applicable anti-KTE-X19 antibodies (see SOA, Section 7.14).

Subjects who are enrolled, but do not receive KTE-X19 treatment, will be followed only until completion of this study and will undergo the following assessments at the time points outlined in the SOA, unless otherwise noted:

- Disease assessment per SOC
- Survival status
- Subsequent therapy for the treatment of CLL/SLL (see Section 6.4)
- AE/SAE reporting (refer to Section 9)
- Concurrent therapies (see Section 6.2)

Subjects may also be contacted by telephone to confirm survival status and subsequent anticancer therapy use. If the subject fails to return to the clinic for a scheduled protocol-specific visit, sites will need to make 2 attempts, using both the telephone and either mail or email to contact the subject. Sites must document both attempts to contact the subject. If a subject does not respond within 1 month after the second contact, then the subject will be considered lost to follow-up, and no additional contact will be required. However, sites will be required to continue to provide survival status as permitted by local regulations.

7.14. Schedule of Assessments

Table 3. Schedule of Assessments

Procedures	Screening	Leukapheresis (Enrollment)	Optional Bridging Therapy	Conditioning chemotherapy			KTE-X19 Administration Period [a]		Post-treatment Follow-up All Post-treatment visits are calculated from Day 0			
Day	≤28 days before enrollment	≤ approx. 5 days after eligibility confirmation		D-5	D-4	D-3	KTE-X19 Infusion D0	D1 to 7[r]	Day 14 (± 2 days)	Day 28 (± 3 days)	Week 8 (± 1 week)	Month 3 (± 2 weeks)
Medical history	X											
Physical exam [a]	X			X			X [a]		X [a]	X	X	X
Weight (plus height at screening)	X	X										
Vital signs [b]	X [b]	X [b]	X						X	X	X	X
ECOG performance status	X											
Neurological assessment [c, k]	X						X [c,k]	QOD[c,k]	X [c,k]			
Disease Assessment	X		X [e,h]							X	*X*[h]	X
ECG	X											
ECHO/MUGA/Chest CT/MRI [d]	X [d]											
CT or MRI [e]	X [e]		X [e]							X		X
Local Labs:												
Pregnancy test (serum or urine)	X	X[r]		X[r]								X
Chemistry panel	X	X	X				X	X	X	X	X	X
CBC w/differential	X	X	X				X	X	X	X	X	X
LDH [f]				X			X [f]	X [f]				
CRP/ferritin [f]		X					X [f]	X [f]				
Lumbar puncture/CSF [g]								*X* [g]	*X* [g]			
Serology (EU sites)[l]	X[l]	X[l]										
Central Labs:												
Bone marrow biopsy and aspirate[h]	X		X[h]							X	*X*[h]	*X*[h]
Optional nodal biopsy [i]	X							D7-14	X			

Procedures	**Screening**	**Leukapheresis (Enrollment)**	**Optional Bridging Therapy**	**Conditioning chemotherapy**			**KTE-X19 Administration Period [a]**		**Post-treatment Follow-up All Post-treatment visits are calculated from Day 0**			
Day	**≤28 days before enrollment**	**≤ approx. 5 days after eligibility confirmation**		**D-5**	**D-4**	**D-3**	**KTE-X19 Infusion D0**	**D1 to 7[r]**	**Day 14 (± 2 days)**	**Day 28 (± 3 days)**	**Week 8 (± 1 week)**	**Month 3 (± 2 weeks)**
Blood draw for Anti-KTE-X19 antibodies [j]		X										X[j]
Blood draw for PBMCs [k]	X							D7[k]	X [k]	X [k]	X [k]	X
Blood draw for Cytokines [k]				X			X	D1,4,7[k]	X [k]	X [k]		X
Lumbar puncture/CSF[g]								*X [g]*	*X [g]*			
Leukapheresis		X [b]										
Bridging Therapy (optional)			X									
Conditioning chemotherapy (Fludarabine/Cyclophosphamide)				X	X	X						
KTE-X19 infusion/Hospitalization							X	X				
AE/SAE[m] / Con meds[n] / Subsequent therapy for CLL/SLL[o] / Survival status[p]	X	X		X	X	X	X	X	X	X	X	X

Table 4. Long-term Follow-up Assessments

Procedure		Long-term Follow-up Period[s] Each visit calculated from Day 0 (± 28 day window)												
Visit frequency	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 21**	**Month 24**	**Month 30**	**Month 36**	**Month 42**	**Month 48**	**Month 54**	**Month 60**	**Month 72, then annually through Year 15**
Physical exam	X	X	X	X	X	X	X							
Disease Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CT or MRI[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bone marrow biopsy and aspirate [h]	X [h]													
Optional nodal biopsy [i]	X													
Local lab:														
CBC w/differential	X	X	X	X	X	X	X	X	X	X	X	X	X	
Central labs:														
Blood draw for PBMC [k]	X	X	X		X		X		X		X		X	X
Blood draw for Anti-KTE-X19 antibodies [j]		*X* [j]												
Targeted / AE/SAEs [m]	X	X	X	X	X	X	X	KTE-X19-related SAEs [n]						
Targeted Con Meds [n]	X	X	X	X	X	X	X							
Subsequent therapy for CLL/SLL[o] / Survival status[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes for Table 3 and Table 4

a **Physical exam (Section 7.5)**: Subjects with new-onset symptoms related to CRS should undergo physical exam at least daily until symptoms resolve to baseline.

b **Vital signs (Section 7.5):** Includes blood pressure, heart rate, respiration rate, oxygen saturation, and temperature. Height will be collected at screening. Vitals will be monitored during and after the KTE-X19 infusion and as clinically indicated. Weight should be taken on the day of leukapheresis.

c **Neurologic assessment (Section 7.7):** A neurological assessment will be performed at screening, on Day 0 prior to KTE-X19 infusion, on Day 1 and every other day during the KTE-X19 hospitalization/observation period, which must last a minimum of 7 days.
- For new onset of neurologic symptoms (eg, severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurologic findings on physical exam), neurologic assessment should be performed at least daily until symptoms resolve to baseline. In addition, brain imaging should be considered.
- Subjects with new onset Grade ≥ 2 neurologic symptoms post-KTE-X19 infusion will have a LP performed to evaluate for potential causes.

d **ECHO/MUGA/Chest CT/MRI**: See Section 7.6 for details.

e **CT or MRI disease assessment (Section 7.8.1)**: Diagnostic quality contrast-enhanced (unless contraindicated) CT (preferred) or MRI of the head, neck, chest, abdomen and pelvis must be performed within 28 days before enrollment to confirm eligibility. Scans obtained as part of SOC before signing of the informed consent form and within 56 days can be used for eligibility. If the subject received treatment for CLL or SLL after the eligibility images were obtained, then additional baseline images must be taken after the completion of CLL/SLL treatment and within 28 days before conditioning chemotherapy. For subjects receiving bridging therapy, baseline images must be taken after bridging therapy is completed or within 48 hours prior to administration of conditioning chemotherapy. Additional images should be performed per the SOA and at any time disease progression is suspected**.** CT Head tumor assessments to be done as clinically indicated, post-Screening. CT Head imaging not required at every visit.

f **LDH/Ferritin/CRP monitoring:** CRP should be collected daily while hospitalized for the KTE-X19 infusion and for subsequent hospitalization for a KTE-X19 related AE. If subject develops CRS or neurological symptoms, LDH and Ferritin should be monitored.

g **Lumbar puncture/CSF (Section 7.7):** Subjects with new onset Grade ≥ 2 neurologic symptoms post-KTE-X19 infusion will have a LP performed to evaluate for potential causes. A portion of the CSF will be submitted to the central lab for evaluation of KTE-X19 levels and cytokines.

h **Bone marrow aspirate and biopsy (Section 7.8.2):** Subjects receiving bridging therapy must have a bone marrow evaluation performed after bridging therapy is completed and prior to administration of conditioning chemotherapy; the screening bone marrow evaluation may be deferred until this time for subjects receiving bridging therapy. Additional bone marrow evaluation must be performed at Day 28 and Month 6; the Month 6 bone marrow evaluation is not required if the subject is confirmed to be MRD- per bone marrow evaluation prior to Month 6; subsequent to Day 28 if a subject's hematologic and radiologic response becomes consistent with CR/CRi with peripheral blood MRD- . Bone marrow evaluation should be considered for persistent cytopenias and to diagnose HLH if appropriate. A bone marrow evaluation should be performed at the time of progressive disease.

i **Optional nodal biopsy (Section 7.8.2):** For subjects who consent to the optional nodal biopsy, the biopsy should be collected at screening, anytime during Day 7 through 14, and at the time of progressive disease.

j **Blood draw for anti-KTE-X19 antibodies:** Baseline antibody samples to be collected prior to start of leukapheresis. If positive at Month 3, additional samples will be collected every 3 months until titers return to baseline, are negative, or up to 12 months post-KTE-X19 infusion

k **Blood draws for PBMCs and cytokines**: During the observation period, PBMCs will be collected on Day 7 and cytokines will be collected on Day 1, 4, and 7.
- Following the initial hospitalization for the KTE-X19 infusion, if the subject is hospitalized with any KTE-X19 related adverse events, blood samples for PBMCs and cytokines will be collected on day of admission, then weekly, and on day of discharge.
- If the subject experiences a Grade ≥ 3 KTE-X19-related toxicity, such as Grade 3 CRS or neurologic event, one additional blood draw for cytokines will be taken at the time of the Grade ≥ 3 KTE-X19-related toxicity and upon resolution of the event.
- If the subject experiences a Grade >/= 2 CRS (per Lee 2014 criteria), an additional cytokine sample should be drawn at the first onset and first reoccurrence of any ≥ grade 2 CRS if not already collected on that day.
- PBMC collection will continue after subject experiences disease progression but remains on study

l **Viral testing for EU sites:** For EU sites, viral serologic tests (eg, HIV, Hep B, Hep C) will be carried out per institution guidelines and EU regulations. Testing may be done within the 30 days prior to leukapheresis and/or on the day of leukapheresis.

m **AE/SAE reporting (Sections 9.2 and Section 9.4): AEs:** After 3 months, only targeted adverse events will be reported in the CRF through 24 months after KTE-X19 infusion or disease progression, whichever occurs first. **SAEs:** After 3 months, only targeted serious adverse events will be reported through 24 months after KTE-X19 infusion or disease progression, whichever occurs first, within 24 hours using the SAE Report Form and in the CRF. Targeted adverse events include central neurological, hematological, infections, GVHD, autoimmune disorders, and secondary malignancies. Subjects who receive an allogeneic SCT will only be followed for KTE-X19 related serious adverse events. Reporting of these SAEs will commence at the time the SCT preparative regimen commences through 24 months after KTE-X19 infusion or disease progression, whichever occurs first, within 24 hours using the SAE Report Form and in the CRF. In addition to the above SAE reporting requirements, anytime a KTE-X19 related SAE occurs it will be reported within 24 hours using the SAE Report Form and in the CRF. All deaths that occur from ICF through end of study will be reported in the CRF.

n **Concomitant medications reporting (Section 6.2):** After 3 months of follow-up, only targeted concomitant medications will be collected for 24 months after KTE-X19 infusion or disease progression, whichever occurs first. Targeted concomitant medications include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations.

o **Subsequent therapy for CLL/SLL (Section 6.4):** Documentation of subsequent therapy for CLL/SLL will continue to be documented while the subject remains on study. Subjects may be contacted by telephone.

p **Survival Status (Section 7.14):** Subjects may be contacted by telephone to confirm survival status.

q **KTE-X19 Administration Period:** refer to Appendix 4 for requirements by country regulatory agencies.

r **Pregnancy test (serum or urine)**: **EU only:** test to be completed within 7 days prior to both Leukapheresis and Conditioning Chemotherapy for females of childbearing potential.

s After completion of at least 3 months of assessments in the KTE-C19-108 study, subjects who received an infusion of KTE-X19 will be provided the opportunity to transition to a LTFU study (KT-US-982-5968) after providing signed informed consent, to complete the remaining time of their LTFU period.

8. SUBJECT WITHDRAWAL

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue to receive study-required treatment and/or other protocol-required procedures at any time during the study while continuing to participate in the study. This is referred to as partial withdrawal of consent.

If partial withdrawal of consent occurs, the investigator must discuss with the subject the appropriate process for discontinuation from the IP, study treatment, or other protocol-required therapies and must also discuss options for continued participation, completion of procedures, and the associated data collection as outlined in the SOA. The level of follow-up and method of communication should also be discussed between the research staff and the subject and documented in the source documents.

Withdrawal of full consent from a study means that the subject does not wish to receive further protocol-required therapy, undergo procedures, and continue participating in study follow-up. Subject data collected up until withdrawal of consent will be retained and included in the analysis of the study. Publicly available data (death records) can be included after withdrawal of consent if local regulations permit. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

As part of the study, sites may be asked to conduct searches of public records, such as those establishing survival status, if available, to obtain survival data for any subject for whom the survival status is not known. Sites may also be asked to retrieve autopsy reports to confirm status of disease at the time of death.

The investigator and/or sponsor can also decide to withdraw a subject from the IP and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

8.1. Reasons for Removal from Treatment

Reasons for removal from protocol-required IP or procedures include any of the following:

- AEs
- Subject request
- Product not available
- Lost to follow-up
- Death
- Decision by sponsor

8.2. Reasons for Removal from Study

Reasons for removal of a subject from the study are as follows:

- Subject withdrawal of consent from further follow-up
- Investigator decision
- Lost to follow-up
- Death

9. SAFETY REPORTING

9.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a relationship with study treatment. The investigator is responsible for ensuring that any AE(s) observed by the investigator or reported by the subject are recorded in the subject's medical record. The definition of AE includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. When recording such events, provide descriptions that the pre-existing condition has changed (eg, more frequent headaches for a subject with pre-existing headaches or blood pressure is now more increased in a subject with pre-existing hypertension).

A pre-existing condition that has not worsened during the study or involves an intervention, such as elective cosmetic surgery or a medical procedure while on study, is not considered an AE.

Interventions for pretreatment conditions (such as elective cosmetic surgery) or medical procedures that were planned before study participation are not considered AEs. Hospitalization for study treatment infusions or precautionary measures per institutional policy are not considered AEs.

The term "disease progression," as assessed by measurement of malignant lesions on radiographs or other methods, should not be reported as AEs. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, CLL).

When an AE or SAE is due to the disease under investigation, it is necessary to report the signs and symptoms. Worsening of signs and symptoms of the malignancy under study should also be reported as AEs in the appropriate section of the CRF.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an AE. If a subject requests to withdraw from protocol-required therapies or the study because of an AE, then the subject should undergo the procedures outlined in the Month 3 visit of the SOA.

9.1.1. Diagnosis Versus Signs and Symptoms

For AEs, a diagnosis (if known) rather than individual signs and symptoms should be recorded on the AE form. The exception is for CRS where both the diagnosis and signs and symptoms will be captured on the CRF AE form. For signs and symptoms of the underlying cancer, the signs and symptoms should be captured. However, on the AE form, the investigator should state that these signs and symptoms are due to the underlying disease.

9.1.2. Abnormal Vital Sign Values

Not all vital sign abnormalities qualify as an AE. A vital sign result must be reported as an AE if it is a change from baseline and meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding if an isolated vital sign abnormality should be classified as an AE. However, if a clinically significant vital sign abnormality is a sign of a disease or syndrome (eg, high blood pressure), only the diagnosis (ie, hypertension) should be recorded on the CRF.

9.1.3. Reporting Abnormal Laboratory Findings

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as AEs. However, abnormal laboratory findings that result in new or worsening clinical sequelae, or that require therapy or adjustment in current therapy, are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

An abnormal laboratory test result must be reported as an AE if it is a change from baseline and meets any of the following criteria:

- Associated with clinical symptoms
- Results in a medical intervention (eg, potassium supplementation for hypokalemia or iron replacement therapy for anemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

9.2. Reporting of Adverse Events

The investigator is responsible for reporting all AEs observed by the investigator or reported by the subject as follows:

Table 5. Reporting Requirements for Adverse Events

Subjects who are enrolled, but do not receive KTE-X19 infusion	Subjects who are enrolled and receive KTE-X19 infusion
Adverse events that occur from enrollment (ie, commencement of leukapheresis) through 30 days after the last study specific procedure (eg, leukapheresis, bridging therapy, CSF prophylaxis, conditioning chemotherapy) or until initiation of a new anticancer therapy, whichever occurs first, will be reported	• AEs that occur from enrollment (ie, commencement of leukapheresis through 3 months after treatment with KTE-X19 infusion will be reported • After 3 months, only targeted AEs will be reported through 24 months after KTE-X19 infusion or disease progression, whichever occurs first, will be reported ○ Targeted adverse events include central neurological events, hematological events, infections, GVHD, autoimmune disorders, and secondary malignancies. • Subjects who receive an allogeneic SCT will only be followed for KTE-X19-related serious adverse events. See Section 9.4 for reporting requirements.

See Section 6.2 for concomitant medication and Section 9.4 for SAE reporting requirements.

The investigator must provide the information listed below regarding the AEs being reported:

- AE diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to IP, conditioning chemotherapy, or study procedures
- Action taken

The AE grading scale used will be the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. A copy of the grading scale can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.cancer.gov). CRS events will be reported using the grading scale outlined in the IB.

In reviewing AEs, investigators must assess whether the AE is possibly related to KTE-X19, bridging therapy, conditioning chemotherapy, any protocol-required study procedure or treatment, disease progression, concurrent disease, concomitant medication, or other. The relationship is indicated by a yes or no response and entered into the CRF. A yes response should indicate that there is evidence to suggest a causal relationship between the study treatment or procedure and the AE. Additional relevant data with respect to describing the AE will be collected in the CRFs.

The investigator is expected to follow reported AEs until stabilization or resolution. If a subject begins a new anticancer therapy, the AE reporting period for non-SAEs ends at the time the new treatment is started.

9.3. Definition of Serious Adverse Events

An SAE is defined as an AE that meets at least 1 of the following serious criteria:

- Fatal
- Life-threatening (places the subject at immediate risk of death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

An AE would meet the criterion of "requires hospitalization" if the event necessitated an admission to a healthcare facility (eg, overnight stay).

Events that require an escalation of care when the subject is already hospitalized should be recorded as an SAE. Examples of such events include movement from routine care in the hospital to the intensive care unit (ICU) or if that event resulted in a prolongation of the existing planned hospitalization.

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as an SAE with the criterion of "other medically important serious event."

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE according to NCI CTCAE criteria; the event itself may be of relatively minor medical significance and, therefore, may not meet the seriousness criteria. Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

Disease progression of the malignancy is not considered an AE. However, signs and symptoms of disease progression may be recorded as AEs or SAEs and indicated as being due to disease progression with the CRF. If the malignancy has a fatal outcome before the end of the SAE reporting period, then the event leading to the death must be recorded as a SAE with the outcome being fatal.

9.3.1. Hospitalization and Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE as described in Section 9.4.

The following hospitalization scenarios are not considered to be serious adverse events:

- Hospitalization for palliative care or hospice care

- Planned hospitalization required by the protocol (eg, for monitoring of the subject or to perform an efficacy measurement for the study)
- Planned hospitalization for a pre-existing condition
- Hospitalization due to progression of the underlying cancer

9.4. Reporting of Serious Adverse Events

The investigator is responsible for reporting all SAEs observed by the investigator or reported by the subject. Unless otherwise indicated in the table below, all SAEs will be reported within 24 hours and recorded in the CRF.

Table 6. Reporting Requirements for Serious Adverse Events

Subjects who screen-fail or who are enrolled, but do not receive KTE-X19 infusion	**Subjects who are enrolled and receive KTE-X19 infusion**
SAEs that occur from signing of the informed consent form through 30 days after the last study specific procedure (eg, screening procedure, leukapheresis, bridging therapy, conditioning chemotherapy) or until initiation of a new anticancer therapy, whichever occurs first, will be recorded in the CRF	• All SAEs that occur from signing of the informed consent form through 3 months after the KTE-X19 infusion or until initiation of another anticancer therapy, whichever occurs first • After 3 months, only targeted SAEs will be reported through 24 months after KTE-X19 infusion or disease progression, whichever occurs first ○ Targeted adverse events include central neurological events, hematological events, infections, GVHD, autoimmune disorders, and secondary malignancies. • Subjects who receive an allogeneic SCT will only be followed for KTE-X19-related serious adverse events from the time the SCT preparative regimen commences through 24 months after KTE-X19 infusion or disease progression, whichever occurs first • All SAEs deemed related to KTE-X19 infusion regardless of time period • All deaths that occur from signing of the ICF through the end of study will be recorded in the CRF

See Section 6.2 for concomitant medication and Section 9.2 for targeted AE reporting requirements.

All SAEs must be submitted to Kite via the eSAE system within 24 hours of the investigator's knowledge of the event. If the eSAE system is unavailable (eg, system outage), then the SAE must be submitted using the SAE Report Form and emailed to the SAE Reporting mailbox: safety_fc@gilead.com.

Subsequently, all SAEs will be reported in accordance with the EU guidelines, or if applicable, as per local reporting guidelines.

Following completion of KTE-C19-108, any relevant information regarding ongoing SAEs must be submitted to Kite Pharma within 24 hours of the investigator's knowledge of the event using the hardcopy format SAE Report Form and sent via e-mail to the SAE Reporting mailbox: safety_FC@gilead.com.

9.5. Reporting Deaths

Death must be reported if it occurs during the SAE reporting period, irrespective of any intervening treatment.

Any death occurring after the first dose of chemotherapy, for the purpose of pre-conditioning, and within 3 months of KTE-X19 infusion, regardless of attribution to treatment, requires expedited reporting within 24 hours. Any death occurring after the SAE reporting period requires expedited reporting within 24 hours only if it is considered related to treatment. Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of underlying leukemia should be recorded as SAEs with the preferred term "chronic lymphocytic leukemia" and must be reported immediately to the sponsor. Death is an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded on the AE form. The term "unexplained death" should be captured if the cause of death is not known. However, every effort should be made to capture the established cause of death, which may become available later on (eg, after autopsy). Deaths during the post-study survival follow-up due to underlying cancer should be recorded only on the Survival Status CRF.

9.6. Pregnancy and Lactation

There is no relevant clinical experience with KTE-X19 in pregnant or lactating women, and animal reproductive studies have not been performed. Women of childbearing potential must have a negative pregnancy test prior to enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. Women of childbearing potential should be monitored according to local and country-specific regulations. This experimental therapy should not be administered to pregnant women or women who are breastfeeding.

Female subjects and female partners of male subjects are recommended to use highly effective contraception (method must achieve an annual failure rate of < 1%) for at least 6 months after conditioning chemotherapy dosing or the administration of KTE-X19, whichever is longer. Male subjects are recommended to not father a child for 6 months after the conditioning chemotherapy dosing or the administration of KTE-X19, whichever is longer. Refer to Appendix 5 for complete list of highly effective contraception methods.

Any pregnancy in a female subject enrolled into the study must be reported, regardless of the time after KTE-X19 infusion. If a pregnancy occurs in either a female subject enrolled into the study or a female partner of a male subject within 6 months of completing conditioning chemotherapy or the administration of KTE-X19, whichever is longer, the pregnancy must be reported. All such pregnancies must be reported to Kite Patient Safety and Pharmacovigilance using the Pregnancy Report Form within 24 hours after becoming aware of the pregnancy. Information regarding the pregnancy and/or the outcome will be requested by the sponsor.

Pregnancy Report Forms should be reported to Kite Patient Safety and Pharmacovigilance at Safety_FC@gilead.com or fax: +1 (650) 522-5477.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons. Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term. Any SAE occurring as an adverse pregnancy outcome after the study has been completed must be reported to Kite Patient Safety and Pharmacovigilance.

The pregnant subject or subject partner should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Kite Patient Safety and Pharmacovigilance using the Pregnancy Outcome Report Form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Kite Patient Safety and Pharmacovigilance.

Pregnancies of female partners of male study subjects exposed to KTE-X19 or other study drugs must also be reported, and relevant information should be submitted to Kite Patient Safety and Pharmacovigilance using the pregnancy and Pregnancy Outcome Report Form within 24 hours. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Kite Patient Safety and Pharmacovigilance.

If a lactation case occurs while the female subject is taking protocol-required therapies, the lactation case must be reported to Kite Patient Safety and Pharmacovigilance within 24 hours after the investigator's awareness of the event using the Special Situations Reporting Form. In addition to reporting a lactation case during the study, investigators should monitor for pregnancy and lactation cases throughout the long-term follow-up period. Report the lactation case and Special Situations Reporting Forms to Kite Patient Safety and Pharmacovigilance at Safety_FC@gilead.com or fax: +1 (650)522-5477.

Any lactation case should be reported to the key sponsor contact within 24 hours of the investigator's knowledge of the event.

9.7. Safety Review Team and Dose-limiting Toxicity

The SRT, that is internal to the study sponsor and in collaboration with at least one study investigator, will be specifically chartered to review safety data during the Phase 1 component of the study and make recommendations on further study conduct and progression of the study based on all data available, including the incidence of KTE-X19 DLT, review of SAEs, and cell expansion of KTE-X19. The SRT safety review outcome will be communicated to the active clinical study sites after the SRT safety review meeting.

DLT is defined as the following KTE-X19-related events with onset within the first 28 days following KTE-X19 infusion:

Table 7. DLT Criteria

DLT	Exceptions
All KTE-X19-related Grade 3 non-hematologic toxicities lasting for > 7 days	• Aphasia/dysphasia or confusion/cognitive disturbance which resolves to at least Grade 1 or baseline within 2 weeks and to at least baseline within 4 weeks. • Fever Grade 3 or 4 • Immediate hypersensitivity reactions occurring within 2 hours of KTE-X19 infusion (related to KTE-X19 infusion) that are reversible to a Grade 2 or less within 24 hours of KTE-X19 infusion with standard therapy • Renal toxicity which requires dialysis for ≤ 7 days • Intubation for airway protection if ≤ 7 days • Tumor lysis syndrome (TLS) including associated manifestations attributable to TLS (eg, electrolyte abnormalities, renal function, hyperuricemia) • Grade 3 transaminase, alkaline phosphatase, bilirubin or other liver function test elevation, provided there is resolution to ≤ Grade 2 within 14 days • Grade 4 transient serum hepatic enzyme abnormalities provided there is resolution to ≤ Grade 3 within < 72 hours • Hypogammaglobulinemia Grade 3 or 4 • Grade 3 nausea and/or anorexia
All KTE-X19-related Grade 4 non-hematologic toxicities regardless of duration	
Grade 4 hematologic toxicity lasting more than 30 days if not attributable to underlying disease	Lymphopenia

CRS will be graded according to a revised grading system {Lee 2014}. AEs attributed to CRS will be mapped to the overall CRS grading assessment for the determination of DLT. Consistent with non-CRS toxicities, all occurrences of Grade 3 CRS of duration > 7 days and all occurrences of Grade 4 CRS are considered DLTs, other than occurrences of CRS due to the exceptions listed above.

A 6 + 3 dose escalation/de-escalation plan was used in the initial Phase 1 DLT evaluation period, Cohort 1 and Cohort 2. Cohort 3 will enroll and dose 3 subjects at a dose of $1x10^6$ anti-CD19 CAR T cells/kg. This is an exploratory cohort. No additional dose levels will be evaluated.
A 3 + 3 design will be used for Cohort 4 SRT evaluation. The initial target dose to be evaluated will be 1×10^6 anti-CD19 CAR T cells/kg (Starting Dose). An additional target dose that may be evaluated in Cohort 4 is 2×10^6 anti-CD19 CAR T cells/kg (Escalation Dose). Escalation to a dose cohort will depend on review of all data available including the number of DLTs within a dose cohort among DLT-evaluable subjects (see Section 10.6). Three to 12 subjects will be enrolled and dosed in Cohort 4. If ≤1 subjects develops a DLT, enrollment will continue to Cohort 4 Escalation Dose. The following table provides details for the dose escalation/de-escalation plan based on the incidences of DLTs for Cohort 1 and Cohort 2.

Table 8. DLT Evaluation Cohort 1 and Cohort 2

Dose Cohort 1 and 2	If incidence of DLT*	Then
1 x 10^6 anti-CD19 CAR T cells/kg (initial dose) (Dose Level 0)	< 2 out of 6	Proceed to Dose Level 1 (2 x 10^6 anti-CD19 CAR T cells/kg)
	= 2 out of 6	enroll 3 more subjects at current dose (Dose Level 0)
	< 3 out of 9	Proceed to Dose Level 1 (2 x 10^6 anti-CD19 CAR T cells/kg)
	≥ 3	Proceed to Dose Level -1 (0.5 x 10^6 anti-CD19 CAR T cells/kg)
0.5 x 10^6 anti-CD19 CAR T cells/kg (Dose Level -1)	< 2 out of 6	Dose Level -1 is the MTD
	= 2 out of 6	Enroll 3 more subjects at current dose (Dose Level -1)
	< 3 out of 9	Dose Level -1 is the MTD
	≥ 3	Additional dose levels lower than Dose Level -1 may be explored
2 x 10^6 anti-CD19 CAR T cells/kg (Dose Level 1)	< 2 out of 6	Dose Level 1 is the MTD
	= 2 out of 6	Enroll 3 more subjects at current dose (Dose Level 1)
	< 3 out of 9	Dose Level 1 is the MTD
	≥ 3	Dose Level 0 is the MTD

The following table provides details for the dose escalation plan based on the incidences of DLTs for Cohort 4.

Table 9. DLT Evaluation Cohort 4

Dose Cohort 4	If incidence of DLT*	Then
1 x 10^6 anti-CD19 CAR T cells/kg (initial dose) (Dose Level 0)	0 out of 3	Proceed to Dose Level 1
	1 out of 3	Enroll 3 more subjects at current dose (Dose Level 0)
	> 1 out of 3 or > 1 out of 6	No MTD is found for cohort 4
	1 out of 6	Proceed to Dose Level 1
2 x 10^6 anti-CD19 CAR T cells/kg (Dose Level 1)	0 out of 3	Dose Level 1 is the MTD
	1 out of 3	Enroll 3 more subjects at the current dose level (Dose Level 1)
	> 1 out of 3 or >1 out of 6	Dose Level 0 is the MTD
	1 out of 6	Dose Level 1 is the MTD

Abbreviations: DLT, dose limiting toxicities; MTD, maximum tolerated dose
*DLT evaluable subjects

For the safe dose level identified, additional subjects will be enrolled and dosed so that the cohort will have up to 9-12 subjects to further evaluate the safety profile.

9.8. Criteria to Pause Enrollment

Study enrollment will be paused in Phase 1 following any grade 5 adverse event that occurs within 30 days of KTE-X19 infusion regardless of attributions.

In the event that the enrollment is paused after the pausing criteria have been met, overall assessment of the benefit/risk ratio will be conducted. If the overall assessment of the benefit/risk ratio is favorable, the study can resume enrollment. Restart of the study may require prior approval if required by applicable regulatory requirements or mandated by in country Regulatory Agency (see Appendix 4).

10. STATISTICAL CONSIDERATIONS

10.1. Hypothesis

No formal hypothesis testing for this phase 1 study.

10.2. Study Endpoints

10.2.1. Primary Endpoints

Incidence of DLTs in subjects treated with KTE-X19 (Section 9.7)

10.2.2. Secondary Endpoints

- Incidence of AEs
- Levels of anti-CD19 CAR T cells in blood
- Overall Response Rate (ORR): The incidence of a CR, CRi, or PR per investigator review as defined by IWCLL 2018 criteria (Appendix 3).

10.2.3. Exploratory Endpoints

- Levels of cytokines in serum
- PK analysis
- Incidence of antibodies to anti-CD19 CAR T cells

For selected safe dose cohort,

- CR/CRi: The incidence of a CR or CRi per investigator review as defined by IWCLL 2018 criteria (Appendix 3).
- MRD^- Rate: The incidence of a minimal residual disease response (MRD−). MRD− is defined as MRD < 10^{-4} per the standard assessment.
- CR/CRi with MRD− (CR/MRD−) Rate: The incidence of MRD− among subjects who have achieved a CR or CRi.
- Duration of Response (DOR): For subjects who experience an objective response including CR, CRi, or PR, DOR is defined as the time from their first objective response to relapse or death in the absence of documented relapse. Subjects not meeting the criteria for progression or death by the analysis data cutoff date will be censored at their last evaluable disease assessment date and their response will be noted as ongoing. Disease assessments obtained and deaths that occur after new anticancer therapies (including allogeneic SCT) will not

contribute to the derivation of duration of response. The DOR for subjects who undergo allogeneic SCT while in remission will be censored at the last evaluable disease assessment prior to the allogeneic SCT; the DOR for subjects who undergo other new anticancer therapies in the absence of documented relapse will be censored at the last evaluable disease assessment prior to the new anticancer therapies.

- Progression-Free Survival (PFS): Defined as the time from the KTE-X19 infusion date to the date of disease progression or death from any cause. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date. Disease assessments obtained and deaths that occur after new anticancer therapies (including allogeneic SCT) will not contribute to the derivation of PFS. The PFS for subjects who undergo allogeneic SCT while in remission will be censored at the last evaluable disease assessment prior to the allogeneic SCT; the PFS for subjects who undergo other new anticancer therapies in the absence of documented relapse will be censored at the last evaluable disease assessment prior to the new anticancer therapies.

- OS: Defined as the time from KTE-X19 infusion to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at their last date known to be alive or the data cutoff date, whichever is earlier.

10.3. Sample Size Considerations

For Cohort 1 and Cohort 2, the study enrolled and dosed a total of 9 subjects with no DLT observed. The anticipated enrollment for Cohort 3 and Cohort 4 is up to approximately 18 subjects, leaving the total up to 27 subjects enrolled and dosed in this study.

Cohort 3 will enroll and dose 3 subjects in an exploratory cohort. No additional subjects will be enrolled or dose levels evaluated.

Cohort 4, the SRT will review all data available including safety and efficacy data after 3 to 6 subjects enrolled and dosed at each dose level (see Section 10.6) have had the opportunity to be followed for 28 days after the KTE--X19 infusion. If the lymphodepleting regimen and one or more KTE-X19 doses evaluated in Phase 1 are determined to be safe based on all data available, including overall safety profile, the incidence of DLT, and cell expansion of KTE-X19, up to approximately total of 12 subjects may be enrolled and dosed in the dose cohort to further evaluate safety. The maximum number of subjects, including those enrolled and dosed in Cohort 4 will be approximately 15 subjects.

10.4. Access to Individual Subject Treatment Assignments

This is a single-arm, open-label study, and subjects and investigators will be aware of treatment received. Data handling procedures for the study will be devised to reduce potential sources of bias and maintain the validity and credibility of the study. These procedures will be outlined in the study statistical plan, SRT charter, and Trial Integrity Document.

10.5. Interim Analysis and Early Stopping Guidelines

During the study, SRT meetings will review the safety and PK data after 3-6 subjects had been dosed at the level of 1 x or 2 x 10^6 anti-CD19 CAR T cells/kg and followed for 28 days.

The SRT will review the safety data and make recommendations on further study conduct and progression of the study as outlined in Section 9.7.

The sponsor reserves the right to conduct additional analyses of safety and efficacy for regulatory interaction purposes. If conducted, no formal hypothesis testing will be performed in such analyses.

10.6. Analysis Subsets

DLT-evaluable set: All subjects treated with the target KTE-X19 dose and followed for at least 28 days, or who received a dose of KTE-X19 lower than the target dose but experienced a DLT during the 28-day post infusion period, up to the time at which a dose level has been evaluated for DLT and deemed safe. Additional Phase 1 subjects enrolled and treated subsequently for the purpose of assessment of the overall safety in the same dose level or a lower dose level will not be considered as part of the DLT-evaluable set, and DLT will not be assessed for such subjects.

Safety analysis set: The safety analysis set is defined as all subjects treated with any dose of KTE-X19.

Full analysis set (FAS): The full analysis set will consist of all enrolled subjects and may be used for the summary of subject disposition and subject listings of deaths.

Modified intent-to-treat (mITT) set: The modified intent-to-treat set will consist of subjects enrolled and treated with KTE-X19 and with radiographically measurable disease after completion of bridging therapy (if applicable) and prior to administration of conditioning chemotherapy. This analysis set will be used for all analyses of objective response, endpoints based on objective response (CR/CRi rate, MRD^- rate, CR/MRD^- rate, DOR, PFS, etc), and OS.

10.7. Planned Method of Analysis

All the analyses will be descriptive. The final analysis will occur when all subjects have completed the study.

10.7.1. ORR

The incidence of objective response and exact 2-sided 95% confidence intervals will be generated.

10.7.2. CR/CRi

The incidence of CR/CRi and exact 2-sided 95% confidence intervals will be generated.

10.7.3. MRD- Rate

The incidence of MRD- rate and exact 2-sided 95% confidence intervals will be generated.

10.7.4. CR/CRi with MRD- (CR/MRD-) Rate

The incidence of CR/MRD- rate and exact 2-sided 95% confidence intervals will be generated.

10.7.5. Duration of Response (DOR)

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for DOR. Estimates of the proportion of subjects remained in response at 3-month intervals will be provided.

10.7.6. Overall Survival (OS)

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for OS. Estimates of the proportion of subjects alive at 3-month intervals will be provided.

10.7.7. Progression-free Survival (PFS)

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for PFS time. Estimates of the proportion of subjects alive and progression-free at 3-month intervals will be provided.

10.7.8. Safety

Subject incidence rates of treatment-emergent adverse events (TEAEs), defined as adverse events with onset on or after the KTE-X19 infusion, will be summarized. TEAEs including all, serious, fatal, CTCAE version 5.0 Grade 3 or higher and treatment-related AEs will be tabulated by preferred term and/or system organ class. CTCAE grade changes in safety laboratory values will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized.

Tables and/or narratives of deaths and treatment related SAEs will be provided.

11. REGULATORY OBLIGATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

11.1. Independent Review Board/Independent Ethics Committee

A copy of the protocol, ICF, and any additional subject or trial information, such as subject recruitment materials, must be submitted to each sites respective Independent Review Board /Independent Ethics Committee (IRB/IEC) for approval. After approval is obtained from the IRB/IEC, all documents must be provided to the key sponsor contact before subject recruitment can begin.

The investigator must also receive IRB/IEC approval for all protocol and ICF changes or amendments. Investigators must ensure that ongoing/continuous IRB/IEC approval (ie, annual approval) is provided throughout the conduct of the study. Copies of IRB/IEC approval are to be forwarded to the key sponsor contact for archiving.

During the course of the study, investigators are to submit site-specific and study SAEs (provided to the site by the key sponsor contact) along with any protocol deviations to their IRB/IEC in accordance with their respective IRB/IEC policies.

11.2. Subject Confidentiality

Subject confidentiality must be maintained within all material that is submitted to the key sponsor contact. The following rules are to be applied.

- Subjects will be identified by a unique identification number.
- Year of birth/age at time of enrollment will be reported according with local laws and regulations.

For reporting of SAEs, subjects will be identified by their respective subject identification number, initials, and year of birth (as per their local reporting requirements for both initials and year of birth).

Per country-specific regulations and ICH/GCP guidelines, investigators, and institutions are required to permit authorization to the sponsor, Contract Research Organization (CRO), IRB/IEC, and regulatory agencies to subject's original source documents for verification of study data. The investigator is responsible for informing potential subjects that such individuals will have access to their medical records, which includes personal information.

11.3. Investigator Signatory Obligations

Each clinical study report will be signed by the coordinating investigator. The coordinating investigator will be identified by Kite Pharma, Inc. under the following criteria:

- Is a recognized expert in the disease setting
- Provided significant contributions to the design or analysis of study data
- Participate in the study and enrolled a high number of eligible subjects

12. PROTOCOL AMENDMENTS AND TERMINATION

If the protocol is amended, the investigator's agreement with the amendment and the IRB/IEC approval of the amendment must be obtained. Documentation acknowledging approval from both parties are to be submitted to the key sponsor contact.

Both Kite Pharma, Inc. and the investigator reserve the right to terminate the investigator's participation in the study as per the terms of the agreement in the study contract. The investigator is to provide written communication to the IRB/IEC regarding either the trial completion or early termination and provide the CRO with a copy of the correspondence.

Kite Pharma, Inc. reserves the unilateral right, at its sole discretion, to determine whether to manufacture KTE-X19 and provide it to sites and subjects after the completion of the study.

13. STUDY DOCUMENTATION AND ARCHIVING

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. The individuals authorized to fulfil these responsibilities should be outlined and included in the Delegation of Authority Form.

Source documents are original documents, data, and records for which the study data are collected and verified. Examples of such source documents may include, but are not limited to, hospital records and patient charts, laboratory, pharmacy, radiology records, subject diaries, microfiches, correspondence, and death registries. Case report form entries may be considered as source data if the site of the original data collection is not available. However, the use of the CRFs as source documentation is not recommended as a routine practice.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all subject records that are readily retrieved to be monitored and or audited at any time by the key sponsor contact, health authorities, and IRB/IECs. The filing system will include at minimum:

- Subject content including ICFs and subject identification lists
- Protocols and protocol amendments, Investigator's Brochure, copies of pre-study documentation, and all IRB/IEC and sponsor communication
- Proof of receipt, experimental treatment flow records, and experimental product-related correspondence.

Original source documents supporting entries into CRFs must be maintained at the site and readily available upon request. No study documents should be discarded without prior written agreement between Kite Pharma, Inc. and the investigator. If storage is no longer available to archive source documents, or if source documents must be moved to an alternative location, the research staff should notify the key sponsor contact prior to shipping the documents.

14. STUDY MONITORING AND DATA COLLECTION

The key sponsor contact, monitors, auditors, or regulatory inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and verifying source documents and records must also assure that subject confidentially is respected.

The monitor is responsible for source document verification of CRF data at regular intervals during the study. Protocol adherence and accuracy and consistency of study conduct and data collection with respect to local regulations will be confirmed. Monitors will have access to subject records as identified in Section 13 (Study Documentation and Archive).

By signing the investigator's agreement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits.

In accordance with ICH GCP and the audit plan, a site may be chosen for a site audit. A site audit would include, but is not limited to, an inspection of the facility(ies), review of subject- and study-related records, and compliance with protocol requirements as well as ICH GCP and applicable regulatory policies.

All data will be collected in an electronic CRF system. All entries must be completed in English and concomitant therapies should be identified by tradenames. For further details surrounding the completion of CRFs, please refer to the CRF completion guidelines.

15. PUBLICATION

Authorship of publications from data generated in ZUMA-8 will be determined based on the uniform requirements for manuscripts submitted to biomedical journals (as outlined in the International Committee of Medical Journal Editors December 2013), which states that authorship should be based on:

- Substantial contributions to the conception or design of the work, acquisition of data, analysis, or interpretation of data for the work; and
- Drafting the article or revising it critically for important intellectual content; and
- Final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work re appropriately investigated or resolved

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. This individual should fully meet the criteria for authorship defined above.

Funding, collection of data, or general supervision of the research alone or in combination does not qualify an individual for authorship.

Any publication, in any form, that is derived from this study must be submitted to Kite Pharma, Inc. for review and approval. The study contract among the institution, principal investigator, and Kite Pharma, Inc. or its delegate will outline the requirements for publication review.

16. COMPENSATION

Kite Pharma, Inc. will provide compensation for study-related illness or injury pursuant to the information outlined in the injury section of the ICF.

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18. APPENDICES

Appendix 1. Sponsor and Investigator Signature Page

KITE PHARMA, INC.
2400 BROADWAY
SANTA MONICA, CA 90404

STUDY ACKNOWLEDGMENT

A Phase 1 Multicenter Study Evaluating the Safety and Tolerability of KTE-X19 in Adult Subjects with Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Amendment 3.0, 01 September 2021

This protocol has been approved by Kite Pharma, Inc. The following signature documents this approval.

Enrique Granados

DocuSigned by:
Enrique Granados
E0BC8099D58C485...

Kite Medical Monitor Name (Printed) | Signature

September 9, 2021 | 12:17:52 AM PDT

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations and guidelines. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Kite Pharma, Inc. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I agree and will ensure that financial disclosure statements will be completed by:

- Me (including, if applicable, my spouse, legal partner and dependent children)
- Subinvestigators (including, if applicable, their spouse, legal partner, and dependent children) at the start of the study and for up to one year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the clinical investigation without prior written consent from Kite Pharma, Inc.

Principal Investigator Name (Printed) | Signature

Date | Site Number

Appendix 2. Binet and Rai Staging Systems for the Classification of CLL

Binet

Stage	Lymph Node Areas	Hemoglobin < 10 g/dL	Platelet < 100 × 10^9/L
A	< 3	No	No
B	≥ 3	No	No
C	±	Either present	

Rai

Stage	Lymphocytosis	Lymph Node Enlargement	Spleen/Liver Enlargement	Hemoglobin < 11 g/dL	Platelet < 100 × 10^9/L
0	Yes	No	No	No	No
I	Yes	Yes	No	No	No
II	Yes	±	Yes	No	No
III	Yes	±	±	Yes	No
IV	Yes	±	±	±	Yes

Appendix 3. IWCLL 2018 Response Criteria and Disease Response Assessment

The determination of CLL response and progression will be based on standardized International Workshop on CLL (IWCLL) 2018 criteria. These criteria will be used to assess SLL.

Appendix Table 1. IWCLL 2018 Response Criteria

Parameter	CR	PR	PD
Group A (indicating tumor load)			
Lymphadenopathy[1]	none ≥ 1.5 cm	decrease ≥ 50%	increase by ≥ 50% or new lymph nodes ≥ 1.5 cm
Hepatomegaly	none	decrease ≥ 50%	Increase by ≥ 50 %
Splenomegaly	none	decrease ≥ 50%	Increase by ≥ 50 %
Blood lymphocytes	< 4000/µL	decrease of ≥ 50% from baseline	Increase by ≥ 50% over baseline[2] to ≥ 5000/µL
Group B (indicating function of the hematopoietic system)			
Platelet count	≥ 100,000/µL	≥ 100,000/µL or increase by ≥ 50% from baseline	Decrease by ≥ 50% from baseline due to CLL
Hemoglobin	≥ 11 g/dL	≥ 11 g/dL or increase by ≥ 50% from baseline	Decrease by ≥ 2 g/dL
Bone Marrow	Normocellular for age, no increase in CLL lymphocytes, no clonal B-lymphoid nodules[3]	CLL cells or clonal B-lymphoid nodules present	Increase in CLL cells by ≥50% on successive biopsies

1 Assessed as sum of the products of up to 6 lymph nodes
2 Subjects with treatment-related lymphocytosis should not be rated PD and remain on study treatment if other criteria for progressive disease are absent.
3 In case of B-lymphoid nodules assessment is recommended to clarify if the population is clonal—if not, subjects can be assessed as CR/CRi if all other criteria are fulfilled.

Appendix Table 2. Disease Response Assessment

Overall Disease Response	Criteria in Appendix Table 1	Additional Criteria
CR	All criteria in Group A and B	No disease related symptoms should be present, neutrophil count ≥ 1500/µL
CRi	All criteria for CR are met except with platelet count <100,000/µl, hemoglobin < 11 g/dL or neutrophil count < 1500/µL	
PR[1]	At least 1 criteria from Group A and 1 from Group B must be fulfilled.	If only one criterion is abnormal at baseline from Group A or B, only that criterion must improve.
SD	Failure to achieve a PR and absence of PD	
PD	Presence of at least 1 of the criteria from Group A or Group B	Constitutional symptoms alone do not define PD. A bone marrow biopsy should be performed to confirm progression if blood count changes are the only evidence of progression.

1 Nodular PR is defined as a CR/CRi with the presence of nodules of clonal lymphocytes in the bone marrow and will be considered a PR for the purposes of this study.

MRD response rate

The MRD response is assessed by evaluation of peripheral blood or bone marrow aspirate with six-color flow cytometry, allele-specific oligonucleotide PCR or high throughput sequencing. MRD negativity is defined as fewer than one CLL cell per 10,000 leukocytes [0.01 %], ie, $<10^{-4}$. Subjects are defined as MRD negative if their disease burden is below this threshold.

Appendix 4. Country specific regulatory agency requirements

France and Italy

The post-infusion monitoring of subjects, described in Section 7.9.3.2.2. of this protocol, will be extended by monitoring on Day 8, Day 9, and Day 10, according to procedures outlined in Table 3, column “KTE-X19 Administration Period, D1 to 7”. The subject may stay hospitalized or return to the clinic daily for this extended monitoring at the discretion of the investigator.

The daily monitoring will include vital signs (see Section 7.5), blood draw for chemistry panel with CRP, blood draw for CBC w/differential, and neurological assessment (see Section 7.7). Any observed toxicity will be managed according to Section 7.10 of this protocol.

Germany

The post-infusion monitoring of subjects, described in Section 7.9.3.2.2. of this protocol, will be extended by monitoring on Day 8, Day 9, and Day 10, according to procedures outlined in Table 3, column "KTE-X19 Administration Period, D 1 to 7". The subject may stay hospitalized or return to the clinic daily for this extended monitoring at the discretion of the investigator.

The daily monitoring will include vital signs (see Section 7.5), blood draw for chemistry panel with CRP, blood draw for CBC w/differential, and neurological assessment (see Section 7.7). Any observed toxicity will be managed according to Section 7.10 of this protocol.

Appendix 5. Birth control methods which may be considered as highly effective[1]

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation[2]:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[2]:
  - oral
  - injectable
  - implantable[3]
- intrauterine device (IUD)[3]
- intrauterine hormone-releasing system (IUS)[3]
- bilateral tubal occlusion[3]
- vasectomized partner [3,4]
- sexual abstinence[5]

1 2014 clinical trial facilitation and coordination group contraception guidance
2 Hormonal contraception may be susceptible to interaction with the investigational product, which may reduce the efficacy of the contraception method
3 Contraception methods that in the context of this guidance are considered to have low user dependency.
4 Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success
5 In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

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 5. Protocols for proposed and on-going studies in RMP part IV

Table 1. Overview of included protocols

Study Number and Title	Protocol Status	Version of Protocol	Date of Protocol Version
Planned studies			
KT-EU-472-6036 Long-term non-interventional study of recipients of Tecartus for treatment of adult patients with relapsed/refractory MCL	Approved	1.2	10 November 2021
ZUMA-3 Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-X19 in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia	Approved	Amendment 7	14 December 2021
KT-EU-474-6644 Long-Term, Non-Interventional Study of the Treatment by Tecartus of Adult Patients with Relapsed or Refractory B-cell ALL	Planned	0.2	31 October 2022

[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
Rainer Heissing	QPPV eSigned	29-Sep-2023 19:39:01
[redacted]	Patient Safety eSigned	29-Sep-2023 21:44:04

Kite Pharma Inc.

NON-INTERVENTIONAL DATA BASE SECONDARY DATA ANALYSIS STUDY PROTOCOL

Study Title	LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF TECARTUS FOR TREATMENT OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA (MCL)
Protocol ID	KT-EU-472-6036
Protocol Version/Date:	Original: 18 February 2021 Version 1.1: 13 July 2021 Version 1.2: 10 November 2021
EU PAS Register No	(will be entered after EU PAS registration)
Clinical Trials.gov Identifier	Study not registered
Active Substance	KTE-X19
Medicinal Product	Tecartus®
Product Reference	EMEA/H/C/005102
Procedure Number	EMEA/H/C/005102
Research Question and Objectives	Primary objective: To evaluate the effectiveness of Tecartus in terms of overall response rate. Secondary objectives: Effectiveness will be evaluated as follows: • To determine the complete remission rate after administration of Tecartus. • To determine the duration of response after administration of Tecartus. • To determine time to next treatment after administration of Tecartus. • To determine the time to relapse or progression of primary disease after administration of Tecartus. • To assess effectiveness of Tecartus by gender and age.

- To assess effectiveness of Tecartus in special populations (patients with prior allogeneic stem cell transplantation [SCT], high-risk relapse or refractory (r/r) MCL patients per Mantle Cell Lymphoma International Prognostic Index [MIPI] score, and CD19 expression status).

Safety will be evaluated as follows:

- To determine the overall survival rate and causes of death after administration of Tecartus.
- To evaluate the incidence rate and severity of adverse drug reactions (ADRs) in patients treated with Tecartus, including secondary malignancies, Cytokine Release Syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, and hypogammaglobulinemia.
- To assess the safety and effectiveness profile by gender, age, and in special populations (high-risk comorbidity index, patients treated with Out of Specifications [OOS] product), additional subgroups may also be explored.
- To assess the risk of tumor lysis syndrome (TLS) and aggravated Graft Versus Host Disease (GvHD), and to detect replication-competent retrovirus (RCR) in samples of patients with secondary malignancies.

Other exploratory objectives:

- To determine the occurrence of loss of target antigen and of functional chimeric antigen receptor (CAR) T-cell persistence in patients relapsing after Tecartus therapy.
- To evaluate pregnancy outcomes in female patients of childbearing potential.

Country (-ies) Of Study

In countries where Tecartus will be authorized. At a minimum UK, Spain, Switzerland and Germany will be countries of study, further countries may be added.

Study Director / Author / Contact Person:

Name: Heribert Ramroth
Telephone: +44 20 8587 2560
Email: Heribert.Ramroth@gilead.com

Marketing Authorization Holder	Kite Pharma EU B.V.	
MAH Contact Person	Name:	Anne-Lise Stanley
	Address:	Kite Gilead Sciences International Ltd Director, Regulatory Affairs Flowers Building Granta Park, Abington Cambridge CB21 6GT, UK
	Telephone: Email:	+44 1223 824642 Anne-Lise.Stanley@gilead.com
Kite EU-Qualified Person Responsible for Pharmacovigilance:	Name: Telephone: Email:	Dr. Anne-Ruth van Troostenburg de Bruyn +49 (0) 89 899 890 181 euqppv@gilead.com

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TABLE OF CONTENTS

LIST OF ANNEXES

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse Event of Special Interest
allo-SCT	allogeneic stem cell transplantation
ANC	Absolute neutrophil count
aRMMs	additional Risk Minimization Measures
ASCT	Autologous stem cell transplant
BOR	Best Overall Response
BTKi	Bruton's tyrosine kinase inhibitor
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CDS	Clinical Data Science
CHMP	Committee for Human Medical Products
CI	Confidence interval
CR	Complete Remission
CRR	Complete Remission Rate
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology of Adverse Events
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of Response
EBMT	European Society for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GLPS	Global Patient Safety
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GvHD	Graft Versus Host Disease
GVP	European Medicines Agency Guidelines on Good Pharmacovigilance Practices
HCP	Health Care Professional
HCT	Hematopoietic cell transplantation
HDT	High dose chemotherapy
HIV	Human immunodeficiency virus
HLA	Human Leukocyte Antigen
HMA	Heads of Medicines Agencies
IL	Interleukin
KM	Kaplan-Meier
mAb	Monoclonal antibody
MAH	Marketing Authorization Holder
MCL	mantle cell lymphoma

MICE	multiple imputation by chained equations
MIPI	Mantle Cell Lymphoma International Prognostic Index
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
MCL	Mantle Cell Lymphoma
OOS	Out of specifications
ORR	Overall Response Rate
OS	Overall survival
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PD	Disease Progression
PMBCL	Primary Mediastinal B-cell Lymphoma
PR	Partial Remission
PSUR	periodic safety update report
QPPV	Qualified Person for Pharmacovigilance
RCR	Replication-competent retrovirus
r/r	relapsed/refractory
SAE	Serious adverse event
SADR	Serious adverse drug reaction
scFv	Single-chain variable fragment
SCT	Stem cell transplantation
SD	stable disease
SSR	Special situation report
TCR	T-cell receptor
TLS	tumour lysis syndrome
US, USA	United States, United States of America

1. RESPONSIBLE PARTIES

Table 1. Table of Responsible Parties

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
Marketing Authorization Holder	Kite Gilead Sciences International Ltd Anne-Lise Stanley Director, Regulatory Affairs Flowers Building Granta Park, Abington Cambridge, CB21 6GT UK	Phone: +44 1223 824642 Email: Anne-Lise.Stanley@gilead.com
Study Director	Heribert Ramroth Sr Director, Clinical Data Science (CDS)/Real World Evidence (RWE) Gilead Sciences International Ltd 2 Roundwood Avenue Stockley Park Uxbridge, UB11 1AF UK	Phone: +44 20 8587 2560 Email: Heribert.Ramroth@gilead.com
Medical Monitor	Jina Shah Senior Director, Safety and Pharmacovigilance Kite Pharma, Inc. 333 Lakeside Drive Foster City, CA 27717-0530 USA	Phone: +1 650 296 3197 Email: jshah4@gilead.com
Biostatistics	Kenny Hu Senior Manager, Biostatistics Kite Pharma, Inc. 333 Lakeside Drive Foster City, CA 27717-0530 USA	Phone: +1 608-774-3021 Email: kenny.hu@gilead.com
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Pharmacovigilance	Global Patient Safety (GLPS) Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 27717-0530 USA	Phone: +1 800 445 3235 Fax: +1 650 522 5477 Email: Safety_fc@gilead.com
EU QPPV	Anne-Ruth van Troostenburg de Bruyn Vice President, GLPS Gilead Sciences GmbH Fraunhoferstr. 17 82152 Martinsried Germany	Phone: +49 (0) 89 899 890 181 Email: euqppv@gilead.com

2. PROTOCOL SYNOPSIS/ABSTRACT

Kite Pharma Inc.

Study Title:	LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF TECARTUS FOR TREATMENT OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA (MCL)
Rationale and Background:	This study will make secondary use of data collected within the infrastructure created by the European Society for Blood and Marrow Transplantation (EBMT) (i.e. the EBMT Registry) to systematically capture information at the time of Tecartus infusion and during follow-up. The follow-up period will be 15 years for the safety part. The effectiveness part will be analyzed once 200 recipients of Tecartus have been documented in the EBMT Registry. The effectiveness part will also include safety assessments and all patients will be included in the safety part. As this study will make secondary use of data collected under 'real-world' conditions, effectiveness and not efficacy will be evaluated. Efficacy can be defined as the performance of an intervention under ideal and controlled circumstances, whereas effectiveness refers to its performance under 'real-world' conditions {Singal 2014}. Rationale for the effectiveness part: To determine effectiveness of treatment with Tecartus, which includes Overall Response Rate (ORR), Complete Remission Rate (CRR) and Duration Of Response (DOR), time to next treatment and time to relapse or progression. Rationale for the safety part: To capture long-term follow-up data for recipients of Tecartus to evaluate the safety, as well as the known and potential risks associated with this product, including incidence rates and severity of adverse drug reactions (ADRs), long term safety, risk of subsequent neoplasm and Overall Survival (OS).

Research Question and Objectives:

The primary objective of this study is as follows:

- To evaluate the effectiveness of Tecartus in terms of overall response rate.

The secondary effectiveness objectives of this study are as follows:

- To determine the complete remission rate after administration of Tecartus.
- To determine the duration of response after administration of Tecartus.
- To determine the time to next treatment after administration of Tecartus.
- To determine the time to relapse or progression of primary disease after administration of Tecartus.
- To assess effectiveness by gender and age.
- To assess effectiveness in special populations (patients with prior allogeneic stem cell transplantation [allo-SCT], high-risk relapse/refractory [r/r] MCL patients per Mantle Cell Lymphoma International Prognostic Index [MIPI] score, and CD19 expression status).

The safety objectives of this study are as follows:

- To determine the overall survival rate and causes of death after administration of Tecartus.
- To evaluate the incidence rate and severity of ADRs in patients treated with Tecartus, including secondary malignancies, Cytokine Release Syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, and hypogammaglobulinemia.
- To assess the safety and effectiveness profile by gender, age, and in special populations (high-risk comorbidity index, patients treated with Out of Specifications [OOS] product), additional subgroups may also be explored.
- To assess the risk of tumor lysis syndrome (TLS) and aggravated Graft Versus Host Disease (GvHD), and to detect replication-competent retrovirus (RCR) in samples of patients with secondary malignancies.

The other exploratory objectives of this study are as follows:

- To determine the occurrence of loss of target antigen and of functional chimeric antigen receptor (CAR) T-cell persistence in patients relapsing after Tecartus therapy.
- To evaluate pregnancy outcomes in female patients of childbearing potential.

Study Design:	This is a long-term, non-interventional study of adult patients with r/r MCL, who have been treated with Tecartus after 2 or more lines of systemic therapy including a Bruton's tyrosine kinase inhibitor (BTKi). Patients' data might be entered into the EBMT Registry up to 1 week prior or anytime following Tecartus infusion. Patients will be followed in the EBMT Registry for both study parts. For the safety part, patients will be followed for up to 15 years; for the effectiveness part, patients will be followed until the first 200 eligible patients treated with Tecartus have been documented in the EBMT Registry (expected approximately 4 years after start of data collection). As this study will make secondary use of data collected in the EBMT Registry, expedited reporting of individual case safety reports will not occur. For the reporting of safety data, the centers will follow the standard spontaneous reporting system per local regulations and timelines.
Population:	The population comprises adult recipients of Tecartus for r/r MCL, at participating centers who consent to have data reported to the EBMT. Patients with underlying organ impairments (e.g. hepatic, renal, cardiac, pulmonary, etc.) will be included in the study analyses. There are no restrictions regarding the patients' performance status of any kind, patients with any grade for Sorror score, Eastern Cooperative Oncology Group (ECOG), and Karnofsky score are allowed. Patients participating in interventional clinical trials at the same time will not be included in the study analyses.
Variables:	This non-interventional, secondary use of data study makes use of the EBMT Registry and is dependent on all needed variables to be collected in the EBMT Cellular and Gene Therapy Form. Furthermore, certain variables may not be generated as part of routine medical practice or local regulations limit the ability to collect the information. • Variables utilized for analysis of the Primary Objective and Effectiveness Objectives — Overall response in terms of complete remission (CR) or partial remission (PR) and date response evaluated — Date of first response (CR or PR) and date of first relapse, progression or death due to any cause

  - — Additional treatment and date of treatment received for primary disease (MCL) after Tecartus administration
  - — Date of the first relapse or progression or significant worsening of the primary disease (MCL) after the Tecartus infusion
- Variables utilized for analysis of Safety Objectives
  - — Date and main cause of death, or date of the last day known being alive
  - — Secondary malignancy (date of diagnosis, type, location and relevant details on biopsy/diagnostic results)
  - — CRS (grade, grade system, date of onset, treatment and resolution status)
  - — Neurologic toxicity (type, grade, grade system, management including treatment, date of onset and resolution status of all neurologic toxicities)
  - — Prolonged cytopenias are defined as inability to recover the absolute neutrophil count (ANC) and platelets within 30 days after the administration of Tecartus. ANC recovery is defined as neutrophil count $\geq 500/mm^3$ for 3 consecutive values, and platelet recovery is defined as platelet count $\geq 50 \times 10^9/L$ without transfusion support within 7 days. Date of recovery will be collected for ANC and platelets.
  - — Serious infections (type, organism, treatment and date of onset of infection as well as resolution status)
  - — Hypogammaglobulinemia is defined as serum IgG levels below 600 mg/dL. Date of onset, treatment, and resolution status will be collected.
  - — Grade, date of onset, treatment and resolution of TLS
  - — Type, date of onset, and resolution status of aggravated GvHD. For acute GvHD in addition: grade and relationship to cell therapy
  - — In case of a secondary malignancy the sampling for RCR testing, the sample date and the test result (not collected in the current EBMT Cellular and Gene Therapy Form)
- Variables utilized for analysis of Other Exploratory Objectives
  - — Date of sampling for loss of target antigen and result (not collected in the current EBMT Cellular and Gene Therapy Form)

  - Data on B-cell recovery as an indirect measure of functional CAR-T persistence: date, B-cell count per volume in peripheral blood, and detection method (not collected in the current EBMT Cellular and Gene Therapy Form)
  - Pregnancy that occurs after administration of Tecartus and additional information related to the outcome of the pregnancy and the newborn's health
- Variables utilized for analysis of exposure to Tecartus
  - Name and dose level of lymphodepleting chemotherapy received prior to Tecartus infusion
  - Tecartus infusion: date, and whether Tecartus was released at physician's request, because the manufactured product was out of specification
- Demographics and Baseline Characteristics
  - Age, gender, and country
  - Height and weight at the time of Tecartus infusion
  - Disease subtype (e.g., classical MCL vs. blastoid MCL)
  - MIPI score at diagnosis
  - CD19 expression status (not collected in the current EBMT Cellular and Gene Therapy Form)
  - Disease status at time of cellular therapy (e.g., sensitive or resistant to chemotherapy or radiation prior to therapy, nodal vs extranodal)
  - Prior lines of treatment and response
  - Disease stage at time of cellular therapy
  - Tumor characteristics (i.e. presence of TP53 mutation and/or17p deletion; Ki-67 index)
  - Time from diagnosis of the primary disease to cellular therapy
  - Prior hematopoietic SCT: autologous or allogeneic, donor human leukocyte antigen (HLA) match type (HLA-identical sibling, syngeneic, HLA-matched other relative, HLA-mismatched relative), source of stem cell product (umbilical cord blood, bone marrow, peripheral blood), immunosuppressants (type and duration), prior GvHD
  - Prior cellular therapy (other than autologous SCT or allo-SCT)
  - Performance score (ECOG or Karnofsky)

- Comorbidities index (Sorror score)
- Active autoimmune, neurologic and hematological disease; infection related complications

For Data Sources: For this specific protocol: patient data as available within the EBMT Registry. For the EBMT Registry: the patient's medical records

Study Size: Effectiveness part:

The first 200 eligible patients who have been treated with Tecartus and documented in the EBMT Registry will be included. Approximately 4 years after the start of data collection 200 patients are expected to have been documented in the EBMT Registry. Based on the gender distribution in MCL, it is expected that 50 female and 150 male patients will be documented at this time point.

Safety part:

All eligible patients who have been treated with Tecartus and documented in the EBMT Registry within 5 years from study start will be included. In addition to the further characterization of the immediate and established toxicities of Tecartus, the study will evaluate rare and delayed safety events occurring in patients during 15 person-years of follow up. The available person-years of follow-up are approximated using a piecewise linear survival curve with 2-year survival rate of 65% (assumption based on the primary analysis of ZUMA-2) and an assumption of long term 15-year survival rate of 35%, indicating an average person-years of follow-up of 8.15 years. Kite also assumes 10% overall loss to follow up, resulting in approximately 2567 total person-years of follow-up. This number of person-years of follow-up will provide 97%, or 82%, or 68%, or 58%, or 50% likelihood of seeing at least one event of interest, if the true rate per 15 years of exposure is at least 1:50, or 1:100, or 1:150, or 1:200, or 1:250, respectively.

Data Analysis: Analysis of all endpoints for this study will include all patients who satisfy the eligibility criteria, are documented within the EBMT Registry and are treated with Tecartus.

Categorical variables will be summarized descriptively by number and percentage of patients in each categorical definition with 95% confidence intervals (CIs). Continuous variables will be summarized descriptively by mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum.

Patient incidence of endpoint events will be provided. Multivariate Poisson regression analyses will be used to estimate cumulative incidence rates adjusted for the follow-up period and predefined characteristics, to estimate their prognostic effect on the outcome.

Kaplan-Meier (KM) curves will be used to illustrate all time-to-event data. The competing risk analysis method will be used for the analysis of time to onset and duration of endpoint events, time to relapse or progression of primary disease and time to next treatment of primary disease, and the cumulative incidence at specified time points will be provided. Cox-proportional hazard models will be used to model multivariate time-to-event data adjusted for predefined characteristics to estimate their prognostic effect on the outcome.

Effectiveness part:

The analysis of the effectiveness endpoints will be conducted when effectiveness data from approximately 200 eligible patients has been documented. Time-to-event endpoints will be analyzed using the KM method (median, 1st quartile, and 3rd quartile along with their 95% CI will be provided as applicable). Cumulative incidence for relapse or progression of primary disease will also be provided using the competing risk method.

- Primary Endpoint
  - Overall response rate
- Effectiveness Endpoints
  - Complete remission rate
  - Duration of response
  - Time to next treatment of the primary disease
  - Time to relapse or progression of the primary disease
  - Effectiveness endpoints by gender and age
  - Effectiveness endpoints in special populations (patients with prior stem cell transplantation, high-risk r/r MCL patients per Mantle Cell Lymphoma International Prognostic Index [MIPI] score, and CD19 expression status)
- Safety Endpoints
  - Overall survival
  - Incidence rates, time to onset, type and location of secondary malignancy
  - Incidence rates, severity, time to onset, management and resolution of CRS

- — Incidence rates, severity, time to onset, management and resolution, and type of neurologic events
- — Incidence rates of prolonged cytopenias and time to recovery of ANC and platelets
- — Incidence rates, type, organism, resolution, and time to onset of serious infections
- — Incidence rates, time to onset of hypogammaglobulinemia, and use of replacement immunoglobulin therapy
- — Safety and effectiveness endpoints on subgroups by gender, age, and in special populations (patients with prior allo-SCT, high-risk comorbidity index, patients treated with OOS product), and additional subgroups may also be explored
- — Incidence rate, severity, resolution, and time to onset of TLS
- — Incidence rate, resolution, time to onset of aggravated GvHD by acute and chronic type; incidence rate, severity and relationship to cell therapy for acute GvHD
- — Frequency of detection of RCR in samples of patients with secondary malignancies

- Other Exploratory Endpoints
  - — Occurrence of loss of target antigen in patients relapsing after Tecartus therapy
  - — Occurrence of functional CAR-T persistence in patients relapsing after Tecartus therapy
  - — Occurrence of pregnancy, and pregnancy outcome among women with childbearing potential

Milestones:

Effectiveness part

Start of data collection:	15 January 2022
End of data collection:	14 June 2025
Study duration:	approximately 4 years
Annual Reports:	annually for 3 years
Final Report:	approximately 4.5 years after start of data collection

Safety part	
Start of data collection:	15 January 2022
End of data collection:	14 October 2041
Study duration:	20 years
Annual Reports:	annually for 5 years, then every 2 years
Final report:	Q1 2043

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPP) and Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

3. AMENDMENTS AND UPDATES

Table 2. Protocol Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1.1	13 July 2021	various	Update	To address the protocol related comments in the PRAC Assessment Report for the Post-Authorisation Measure ANX 002 and to implement the respective changes
1.2	10 November 2021	various	Update	To address the protocol related comment in the PRAC Assessment Report for the Post Authorisation Measure ANX 002 and to implement the respective changes

Protocol Modifications

Protocol modifications may only be made by Kite Pharma Inc., a wholly owned subsidiary of Gilead Sciences, Inc. Any planned amendments will be discussed with the regulatory authority and the European Society for Blood and Marrow Transplantation (EBMT) prior to implementation.

4. MILESTONES

Table 3. Protocol Milestones

Milestone	Planned Date
PRAC approval of study protocol	30 September 2021
Protocol registration in the EU PAS Registry	2 weeks after PRAC approval
Start of data collection*	15 January 2022
End of data collection effectiveness part**	14 June 2025
End of data collection safety part***	14 October 2041
Analyses of published literature and databases for comparator	5 years following start of data collection
Study duration	20 years
Safety Data Reports	Quarterly reports will be generated on the basis of quarterly data transmission from EBMT. The reports will be appended to the 6 monthly PSURs, unless a quarterly report generates an urgent new safety finding, resulting in submission as a stand-alone report in between PSUR cycles. 2022 to 2026, frequency thereafter to be re-evaluated
Annual reports effectiveness part	Q3 2022 to 2024 annually
Annual reports safety part	Q1 2023 to 2027 annually, then every 2 years
Final report of study results	Q1 2043

* As the data collection in the EBMT Registry is independent of this study (secondary use of data), the start of data collection is the date from which data extraction starts. First data extraction for study KT-EU-472-6036 will take place 3 months after protocol registration or contract execution with the EBMT, whichever comes last.
** When effectiveness data from approximately 200 eligible patients are documented.
*** 20 years after protocol registration, no further data will be included in the study analyses.

5. RATIONALE AND BACKGROUND

5.1. Rationale for the Current Study

T cells play a central role in the immune system by destroying diseased cells, including tumor cells, throughout the body {Kershaw 2013}. Studies with tumor vaccines {Kantoff 2010}, immune checkpoint inhibitors {Hamid 2013, Wolchok 2013}, tumor infiltrating lymphocytes {Rosenberg 2011}, the bispecific cluster of differentiation 19 (CD19)-directed CD3 T-cell engager blinatumomab {BLINCYTO 2019}, and chimeric antigen receptor (CAR) T-cells {KYMRIAH 2018, YESCARTA 2019a, YESCARTA 2019b} have demonstrated the potential of T cells to treat cancer.

Engineered autologous T cell immunotherapy, which uses a patient's own immune cells, offers a promising approach for treating many types of cancer. One type of engineered autologous T cell therapy comprises T cells that have been engineered ex vivo to express a CAR directed toward a tumor surface antigen. These CARs are fusion proteins with antigen-binding, transmembrane, and T cell activation domains that, when expressed in T cells, can target tumor antigens for T cell-mediated killing {Kershaw 2013}. CAR T cells have demonstrated promising antitumor activity across numerous B-cell malignancies, including non-Hodgkin lymphoma {Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017a, Kochenderfer 2017b, Locke 2019, Neelapu 2017, Turtle 2016}, chronic lymphocytic leukemia {Kochenderfer 2015, Porter 2015, Porter 2011}, and acute lymphoblastic leukemia {Davila 2014, Gupta 2007, Lee 2015, Maude 2014, Maude 2015, Singh 2016}.

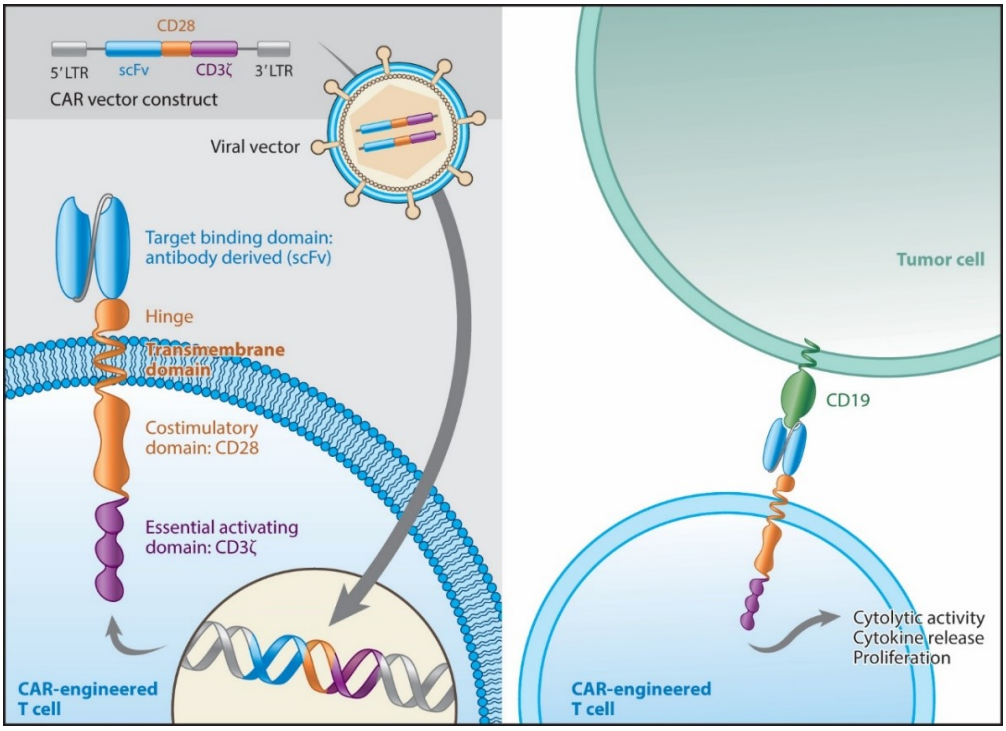
5.1.1. Anti-CD19 CAR T-cell Product: Tecartus

Tecartus is an autologous CAR T-cell therapy that targets CD19, a 95 kD transmembrane protein that is uniquely expressed in normal B cells and in most B-cell malignancies {Anderson 1984, Johnson 2009, Leonard 2001, Nadler 1983, Olejniczak 2006, Rodriguez 1994, Uckun 1988}. Expression occurs beginning at the pro-B-cell stage and continues throughout B-cell differentiation {Anderson 1984, Nadler 1983, Uckun 1990, Uckun 1988}, but is down regulated in plasma cells {Gupta 2009, Lin 2004}. Specifically, CD19 expression is maintained in MCL {Argatoff 1997, Cabezudo 1999, Ginaldi 1998, Leonard 2001, Marcondes 2017, Martinez 2003, Yang 2005}.

Kite Pharma, Inc. has developed manufacturing processes to meet the needs of patients with different types of B-cell malignancies. Tecartus has been developed for the treatment of diseases with circulating $CD19^+$ tumor cells such as leukemias and MCL. Tecartus is currently approved in the United States (US) for the treatment of adult patients with relapsed/refractory (r/r) MCL and in the European Union (EU) for the treatment of adult patients with r/r MCL after 2 or more lines of systemic therapy including a Bruton's tyrosine kinase inhibitor (BTKi).

The structure of the anti-CD19 CAR construct used for production of Tecartus and the product's mechanism of action are shown in Figure 1. Briefly, the construct comprises the following domains: an anti-human CD19 single-chain variable region fragment (scFv) region; the partial extracellular domain and complete transmembrane and intracellular signaling domains of human CD28; and the cytoplasmic portion, including the signaling domain, of human CD3ζ, a component of the T-cell receptor (TCR) complex {Kochenderfer 2009}.

Figure 1. Tecartus CAR Construct and Mode of Action



Abbreviations: CAR, chimeric antigen receptor; CD, cluster of differentiation; LTR, long terminal repeat; scFv, single-chain variable region fragment
General notes: The left panel illustrates the Tecartus construct with scFv/CD28/CD3ζ, which is inserted in a replication-incompetent γ -retroviral vector and, upon transfection of T cells, expresses the chimeric transmembrane protein. The right panel illustrates the anti-CD19 CAR T-cell binding to its target CD19 on the tumor cell surface.

The CAR antigen-binding domain is a scFv derived from the FMC63 murine monoclonal antibody (mAb) directed against human CD19{Nicholson 1997}. This antigen-binding domain extends from the engineered T-cell membrane into the extracellular space, where it can recognize CD19, its target antigen. The antigen-binding domain of the anti-CD19 CAR construct encompasses the following domains, in order from the N-terminal end towards the membrane proximal region: the FMC63 antibody light-chain variable domain (complementary determining regions [CDR] 1 and 2); a peptide linker {Cooper 2003}; and the FMC63 antibody heavy chain variable domain (CDR1, CDR2, and CDR3). This folding retains the selectivity and affinity of the parent FMC63 mAb. Extensive comparative analyses {Nicholson 1997} demonstrated that the specificity of the scFv was equivalent to that of the original FMC63 mAb {Zola 1988, Zola 1991, Zola 1989}. Kinetic studies with radiolabeled material showed that the scFv binds target cells with a dissociation constant of 2.3×10^{-9}, which is comparable to the dissociation constant of 4.2×10^{-9} for the parent mAb {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 {Roberts 2018}. The intracellular signaling domain of CD28 provides a costimulatory signal that works in concert with the primary CD3ζ signal to augment T-cell function, including interleukin-2 production {Finney 1998}. Together, these signals stimulate proliferation of the CAR T cells and direct the 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}.

Kite is conducting a Phase 2, multicenter, open-label study (hereafter referred to as ZUMA-2) to evaluate the safety and efficacy of Tecartus in subjects with r/r MCL.

Eligible patients had disease progression after last regimen or refractory disease to the most recent therapy. All subjects had to have received up to 5 prior lines of therapy, which included a regimen with anthracycline or bendamustine, an anti-CD20 mAb, and a Bruton's tyrosine kinase inhibitor (BTKi) treatment. The study excluded patients who had previously undergone allogeneic stem cell transplantation (allo-SCT), detectable malignant cells in the cerebrospinal fluid or brain metastases, any history of central nervous system lymphoma or central nervous system disorders, and active or serious infections.

5.1.2. Outcome of Patients Treated With Tecartus in ZUMA-2

Treatment of r/r MCL with anti-CD19 CAR T cells results in a high response rate with durable remissions. The primary endpoint of the ZUMA-2 study was to evaluate the efficacy of Tecartus, as measured by the ORR. Based on a central assessment per Lugano Classification {Cheson 2014} in the inferential analysis set (n=68), the ORR was 93% with a CR rate of 67%, demonstrating that the primary endpoint of ZUMA-2 was met {Wang 2020}. Among 42 subjects who initially had a PR or stable disease (SD), 24 subjects (57%) went on to achieve a CR after a median of 2.2 months (range: 1.8 to 8.3 months). Of the 24 subjects whose responses improved over time, 21 subjects converted from PR to CR, and 3 subjects converted from SD to CR.

Administration of CAR T cells carries a number of risks independent from the type of target because the immune reaction against tumor cells can elicit a generalized reaction that include fever, hypotension, respiratory failure, and death {Brudno 2016}. These toxicities are defined as CRS and generally occur within the first week from treatment (Table 4). Lee, et al, proposed a grading system based on the number of affected organs, severity, and therapeutic approaches needed, ie, vasopressors or ventilatory support {Lee 2014}. In the modified grading scale, neurologic toxicities were not reported as part of CRS. Individual symptoms of CRS were graded for severity using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and linked to the corresponding CRS episode. Neurologic toxicities can occur in the absence of CRS, concurrently with CRS, or after CRS has resolved, and the symptoms include fine tremors, aphasia, and seizures (Table 5) {Brudno 2016, Lee 2014, Park 2016}. Prolonged cytopenias, infections, and hypogammaglobulinemia were also observed in ZUMA-2.

CRS following treatment with Tecartus infusion occurred in 91% of patients. Fifteen percent (15%) of patients experienced Grade 3 or higher (severe or life-threatening) CRS. The median time to onset was 3 days (range: 1 to 13 days) and the median duration was 10 days (range: 1 to 50 days). All patients (100%) recovered from CRS.

Neurologic adverse reactions following treatment with Tecartus infusion occurred in 68% of patients. Thirty-three percent (33%) of patients experienced Grade 3 or higher (severe or life-threatening) adverse reactions. The median time to onset was 8 days (range: 1 to 262 days). Neurologic events resolved for 47 out of 56 patients with a median duration of 13 days (range: 1 to 567 days). Three patients had ongoing neurologic events at the time of death, including one patient with the reported event of serious encephalopathy and another patient with the reported event of serious confusional state. The remaining unresolved neurologic events were Grade 2. Eighty-five percent of all treated patients experienced the first CRS or neurological event within the first 7 days after Tecartus infusion.

Table 4. Selected Signs and Symptoms of Cytokine Release Syndrome

Signs and Symptoms of Cytokine Release Syndrome
Pyrexia
Hypotension
Hypoxia
Chills
Tachycardia
Headache
Alanine aminotransferase increased
Aspartate aminotransferase increased
Fatigue
Nausea
Diarrhea

Table 5. Selected Signs and Symptoms of Neurologic Events

Signs and Symptoms of Neurologic Events
Encephalopathy
Tremor
Confusional State
Aphasia
Somnolence
Lethargy
Agitation
Disturbance in attention
Memory impairment
Seizure
Delirium
Dysarthrias

Tecartus manufacturing relies on a replication incompetent murine γ-retroviral vector to stably integrate the anti-CD19 CAR transgene into the T-cell genome, thus creating a theoretical risk of oncogenesis via insertional mutagenesis or replication-competent retrovirus (RCR). However, numerous clinical studies in patients with hematologic malignancies or solid tumors and in patients infected with human immunodeficiency virus (HIV) showed no overt genotoxic effects manifested by development of subsequent neoplasms following infusion of T cells that had been transduced with replication incompetent γ-retroviruses encoding a therapeutic TCR or CAR. These findings represent data from 86 unique patients with hematologic malignancies or solid tumors who exhibited clinical benefit and have follow-up ranging from 3 months to 4.8 years {Brentjens 2013, Kochenderfer 2016, Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017a, Robbins 2015}. One of these studies (Study NCI 09-C-0082) is ongoing and has shown no evidence of secondary malignancy over a period of up to 24 months of follow-up in a total of 43 patients with advanced B-cell malignancies {Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017a}. Further analysis of Study NCI 09-C-0082 by Kite showed no evidence of secondary malignancies resulting from the infusion of the anti-CD19 CAR T cells at a median follow-up of 36 months (range: 13 to 78 months) (Kite, data on file). These patients were treated with retrovirally transduced T cells expressing the same CAR as utilized in Tecartus. Data from Study KTE-C19-101 (ZUMA-1) in 101 patients with r/r large-cell lymphomas and using Kite's first approved CAR T-cell therapy, Yescarta, which uses the same retroviral vector, producer clone, and anti-CD19 CAR construct as used for Tecartus, showed no reports of malignancies related to the anti-CD19 CAR T-cell after a median follow-up of 27.7 months {Locke 2019}.

In the HIV clinical studies, no treatment-related malignancies have been observed among more than 40 patients with HIV who were treated and followed for a period of 1 to 11 years {Scholler 2012}. Notably, Scholler and colleagues have shown that CAR T cells were detected in 98% of postinfusion samples over this period. This analysis represented over 540 patient-years of accumulated follow-up and showed no clinical evidence of viral vector integration-mediated toxicity.

Additionally, a comprehensive summary of RCR data derived from patients treated with T cells transduced ex vivo with murine γ-retroviral vectors was performed on 629 follow-up samples obtained 1 month to 8 years after infusion {Bear 2012}. The data demonstrated a lack of RCR events in patient samples, including samples from HIV-infected patients, across 29 clinical studies. Due to a lack of detectable RCR in patients, the authors further concluded that infectious and replication-competent γ-retroviral vector particles used to modify the patient's own T cells are not shed via saliva, urine, or feces into the environment and, therefore, do not represent any risk to organisms present in the environment. Additional vector integration site analyses conducted by the sponsor support the low risk of insertional mutagenesis in patients treated with engineered T-cell products {Chang 2019}.

Taken together, the clinical studies described above suggest that T-cell transformation due to γ–retroviral or lentiviral insertional mutagenesis is an extremely rare event that likely requires the contribution of multiple additional factors beyond the integration site of the viral vector.

The purpose of this study is to analyze and report on the follow-up data for recipients of Tecartus captured in the EBMT Registry to address the effectiveness of this product based on ORR, CRR and DOR, and to describe the long-term safety including incidence rates and severity of adverse drug reactions (ADRs), the risk of subsequent neoplasm, OS, time to next treatment and time to relapse or progression.

The EBMT is a non-profit organization that was established in 1974 to allow scientists and physicians involved in clinical bone marrow transplantation to share their experiences and develop cooperative studies. More recently, the scope of the organization has broadened to include work in cellular therapy as well. The EBMT has created a specific cell therapy module of its registry and utilizes the infrastructure created for the SCT registry to systematically capture data on all cell therapies. This study will use the data accrued on Tecartus in the EBMT Registry to systematically evaluate information on patients who receive Tecartus.

6. RESEARCH QUESTIONS AND OBJECTIVES

This is a long-term, non-interventional effectiveness and safety study of adult patients with r/r MCL after 2 or more lines of systemic therapy including a BTKi, who have been treated with Tecartus.

The study will utilize follow-up data for recipients of Tecartus to determine the effectiveness including ORR, CRR and DOR, and to evaluate the long-term safety including incidence rates and severity of adverse drug reactions (ADRs), the risk of subsequent neoplasm, OS, time to next treatment and time to relapse or progression.

Therefore, the study will make secondary use of the data captured in the EBMT Registry, using the infrastructure EBMT created for the SCT registry, to systematically capture information at the time of Tecartus infusion and for up to 15 years of follow-up in the safety part. Follow-up for the effectiveness part will be stopped once the first 200 eligible patients treated with Tecartus have been documented in the EBMT Registry, and this timepoint is expected to occur approximately 4 years after start of data collection. The effectiveness part will also include safety assessments and all patients will be included in the safety part.

As this study will make secondary use of data collected under ‘real-world' conditions, effectiveness and not efficacy will be evaluated. Efficacy can be defined as the performance of an intervention under ideal and controlled circumstances, whereas effectiveness refers to its performance under ‘real-world' conditions {Singal 2014}.

The primary objective of this study is:

- To evaluate the effectiveness of Tecartus in terms of overall response rate.

The secondary effectiveness objectives of this study are:

- To determine the complete remission rate after administration of Tecartus.
- To determine the duration of response after administration of Tecartus.
- To determine the time to next treatment after administration of Tecartus.
- To determine the time to relapse or progression of primary disease after administration of Tecartus.
- To assess effectiveness by gender and age.
- To assess effectiveness in special populations (patients with prior allogeneic stem cell transplantation [SCT], high-risk r/r MCL patients per Mantle Cell Lymphoma International Prognostic Index [MIPI] score, CD19 expression status).

The safety objectives of this study are:

- To determine the overall survival rate and causes of death after administration of Tecartus.
- To evaluate the incidence rate and severity of ADRs in patients treated with Tecartus, including secondary malignancies, Cytokine Release Syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, and hypogammaglobulinemia.
- To assess the safety and effectiveness profile by gender, age, and in special populations (high-risk comorbidity index, patients treated with Out of Specifications [OOS] product), additional subgroups may also be explored.
- To assess the risk of tumor lysis syndrome (TLS) and aggravated Graft Versus Host Disease (GvHD), and to detect of replication-competent retrovirus (RCR) in samples of patients with secondary malignancies.

The other exploratory objectives of this study are as follows:

- To determine the occurrence of loss of target antigen and of functional CAR-T persistence in patients relapsing after Tecartus therapy.
- To evaluate pregnancy outcomes in female patients of childbearing potential.

7. RESEARCH METHODS

7.1. Study Design

This study is a long-term, non-interventional effectiveness and safety study planned to evaluate outcomes of adult patients with r/r MCL after 2 or more lines of systemic therapy including a BTKi, who have been treated with Tecartus, in the post-marketing setting making secondary use of data available in the EBMT Registry. The EBMT centers enter data into the EBMT Registry following the EBMT specific procedures and requirements. According to the EBMT monitoring plan the site is responsible for completing the data collection forms within 6 weeks after a patient visit. The preferred and most common option to enter data into the EBMT Registry is direct electronic data entry by a trained and authorized staff member from the center. This option ensures immediate access of the center's data by the EBMT and authorized users. Alternatively, direct data entry by a national registry on behalf of specific centers that submit paper forms to this national registry is possible. Patients' data may be entered up to 1 week prior or anytime following administration of Tecartus infusion. Data entry into the EBMT Registry requires signed informed consent by the patient or a legal guardian to allow data to be provided to the EBMT. Patients will be followed in the EBMT Registry for both study parts. For the safety part for up to 15 years; for the effectiveness part until the first 200 eligible patients treated with Tecartus have been documented in the EBMT Registry (which is expected to be approximately 4 years after the start of data collection).

7.2. Setting

No treatments, therapy protocols, or procedures are mandated. There is no prescribed visit schedule. Data entered into the EBMT Registry will be obtained from clinical, laboratory, and diagnostic assessments conducted during the course of routine medical practice and available in the patient's medical chart, collected for the primary purpose of patient care. Data will be captured by completion of the EBMT Cellular and Gene Therapy Form for the time points described below (see 7.6), using the most current data available.

Data entry into the EBMT Registry will be done by the EBMT centers irrespective of this study according to EBMT guidance documents in its most current versions (e.g. submitting data to the EBMT).

The EBMT Cellular and Gene Therapy Form was created in close cooperation with the Committee for Human Medical Products (CHMP) and other relevant Marketing Authorization Holders (MAHs). The aim is not to collect all possible information from the medical charts, but to collect the essential information in the EBMT Registry. For safety data, the forms specifically collect data on events of special interest. There is also an option to add other complications/toxicities in the EBMT Registry. The EBMT therefore collects a defined data set as specified in the EBMT Cellular and Gene Therapy Form. The EBMT Cellular and Gene Therapy Form is under the control of the EBMT, and therefore its content may change throughout the course of the study.

Available data within the EBMT Registry will be analyzed for this study at defined time points. In this registry only predefined data of interest will be collected from the medical charts.

Spontaneous ADR reporting independent from this study is the primary source for detecting new safety concerns/signals. New emerging safety concerns and respective data/variables might be added throughout the course of the study on the EBMT Cellular and Gene Therapy Form to support structured data collection of such new relevant data during the study, if agreed by the EBMT, who owns this form.

7.2.1. Eligibility

The EBMT Registry collects data on all patients receiving cell therapy. Eligible patient data for this study is from adult patients treated with Tecartus for r/r MCL after 2 or more lines of systemic therapy including a BTKi, irrespective of whether the Tecartus product was within approved product specifications or out of specifications, but released at physician's request. Eligible patient data includes data of patients with underlying organ impairments (e.g., hepatic, renal, cardiac, pulmonary, etc.) and with any grade for Sorror score, ECOG and Karnofsky score, i.e. there are no restrictions regarding the patients' performance status of any kind.

Patients participating in interventional clinical trials at the same time will not be included in this study analyses.

7.2.2. Study Centers

All centers that are qualified for the use of Tecartus and who provide their data to the EBMT Registry contribute to this study. The centers enter the data directly via the EBMT Cellular and Gene Therapy Form into the EBMT Registry following the EBMT data entry guidance documents (see Section 7.2). The centers will enter initial patient data and any subsequent follow up data.

In a commercial setting, Kite is engaging with sites at time of initial commercial center qualification process to allow the prescribing of Tecartus and when Kite delivers training on the required additional risk minimization measures (aRMMs). Kite cannot engage in EBMT Registry management related interactions with the centers.

These commercial sites are generally members of EBMT and therefore Kite has non study/registry-related contacts with sites. Nevertheless, because of the responsibilities of Kite to deliver training to qualified prescriber sites, the contact with centers that are contributing to the EBMT Registry can be used to deliver relevant reminders on the importance of spontaneous reporting and that this is not replaceable by reporting into the EBMT Registry.

7.3. Variables

This secondary use of data study makes use of the EBMT Registry and is dependent on all needed variables to be collected in the EBMT Cellular and Gene Therapy Form. Furthermore, certain variables may not be generated as part of routine medical practice or because local regulations limit the ability to collect the information.

The EBMT Cellular and Gene Therapy Form specifies the sub-set of data that are transcribed by the centers from the patients' medical charts into the EBMT Registry.

7.3.1. Variables utilized for analysis of Primary Objective and Effectiveness Objectives

- Overall response in terms of complete remission (CR) or partial remission (PR) and date response evaluated.
- Date of first response (CR or PR) and date of first relapse, progression or death due to any cause.
- Additional treatment and date of treatment received for primary disease (MCL) after Tecartus administration
- Date of the first relapse or progression or significant worsening of the primary disease (MCL) after the Tecartus infusion

7.3.2. Variables utilized for analysis of Safety Objectives

The EBMT Registry will collect the variables listed and this study will utilize this data for analysis.

- Date and main cause of death, or date of the last day known being alive
- Secondary malignancy is defined as the development of any new malignancies occurring after the administration of Tecartus. The date of diagnosis, type, location and relevant details on biopsy/diagnostic results will be collected.
- CRS is a class effect of CAR T-cell therapies, which may occur at different grades of severity, characterized by fever, rigors, nausea, emesis, headache, hypotension, and pulmonary, hepatic, and renal dysfunction. CRS grade (Table 6), system of grading, date of onset, treatment and resolution status will be collected.
- Neurologic toxicity is a class effect of CAR T cell therapies and most commonly includes confusion, delirium, aphasia, obtundation, myoclonus, and seizures. The type, grade, system of grading (Common Terminology of Adverse Events [CTCAE] or ICANS score), treatment, date of onset and resolution status of all neurologic toxicities will be collected.

- Prolonged cytopenias are defined as inability to recover the absolute neutrophil count (ANC) and platelets within 30 days after the administration of Tecartus. ANC recovery is defined as neutrophil count ≥ 500/mm^3 for 3 consecutive values, and platelet recovery is defined as platelet count ≥ 50 ×10^9/L without transfusion support within 7 days. The date of recovery for ANC and platelets will be collected.

- Serious infections are defined as viral, bacterial or fungal infections that require intervention or have led to a negative outcome for the patient (including death) as determined by the treating physician and reported to the EBMT Registry. The type, organism, treatment and date of onset of infection and resolution status will be collected.

- Hypogammaglobulinemia is defined as serum IgG levels below 600 mg/dL. For hypogammaglobulinemia the date of onset, treatment, and resolution status will be collected.

- Grade, date of onset and resolution of TLS

- Type, date of onset, and resolution status of aggravated GvHD. For acute GvHD in addition: grade and relationship to cell therapy

- In case of a secondary malignancy the sampling for RCR testing, the sample date and the test result (not collected in the current EBMT Cellular and Gene Therapy Form)

Table 6. Grading of CRS

Grade[1]	Sign/Symptom/Intervention
1	Symptoms are not life-threatening and require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)
2	Symptoms require and respond to moderate level of intervention: Oxygen requirement < 40% FiO_2, or Hypotension responsive to intravenous fluid infusion or low dose of one vasopressor, or Grade 2 organ toxicity[2]
3	Symptoms require and respond to aggressive intervention: Oxygen requirement > 40% FiO_2, or Hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity or Grade 4 transaminitis
4	Life-threatening symptoms Requirement for mechanical ventilatory support, or Grade 4 organ toxicity (excluding transaminitis)
5	Death

1 CRS grading adapted from Lee, et al {Lee 2014}
2 Organ toxicities are defined according to National Cancer Institute (NCI) Common Terminology of Adverse Events (CTCAE).

7.3.3. Variables utilized for analysis of Other Exploratory Objectives

The analyses of other exploratory objectives depend on changes to the variables collected in the EBMT Cellular and Gene Therapy Form and their availability within the EBMT Registry.

- Date of sampling for loss of target antigen and result (not collected in the current EBMT Cellular and Gene Therapy Form)
- Data on B-cell recovery as an indirect measure of functional CAR-T persistence: date, B-cell count per volume in peripheral blood, and detection method (not collected in the current EBMT Cellular and Gene Therapy Form)
- The EBMT Registry will collect data on any pregnancy that occurs after administration of Tecartus and additional information related to the outcome of the pregnancy and the newborn's health, and this study will utilize this data for analysis.

7.3.4. Variables for exposure to Tecartus

- Name and dose level of lymphodepleting chemotherapy received prior to Tecartus infusion.
- Tecartus infusion: date, and whether Tecartus was released at physician's request, because the manufactured product was out of specification.

7.3.5. Variables to Collect for Demographics and Baseline Characteristics

- Age, gender, and country
- Height and weight at the time of Tecartus infusion
- Disease subtype (e.g., classical MCL vs. blastoid MCL)
- MIPI score at diagnosis
- CD19 expression status (not collected in the current EBMT Cellular and Gene Therapy Form)
- Disease status at time of cellular therapy (e.g., sensitive or resistant to chemotherapy or radiation prior to therapy)
- Prior lines of treatment and response
- Disease stage at time of cellular therapy
- Tumor characteristics (i.e. presence of TP53 mutation and/or 17p deletion; Ki-67 index)
- Time from diagnosis of the primary disease to cellular therapy

- Prior hematopoietic cell transplantation: autologous or allogeneic, donor HLA match type (HLA-identical sibling, syngeneic, HLA-matched other relative, HLA-mismatched relative), source of stem cell product (umbilical cord blood, bone marrow, peripheral blood), immunosuppressants (type and duration), prior GvHD
- Prior cellular therapy (other than autologous or allogeneic SCT)
- Performance score (ECOG or Karnofsky)
- Comorbidities index (Sorror score)
- Active autoimmune, neurologic and hematological disease; infection related complications

7.4. Data Sources

The source data for the EBMT Registry will be the data presented in the patients' medical records. A sub-set of these data from patients' medical records will be transcribed by the centers in the EBMT Registry utilizing the EBMT Cellular and Gene Therapy Form (Annex 5). The data on patients receiving Tecartus available in the EBMT Registry will be the data source for this study.

The EBMT maintains a registry which encompasses all haematopoietic stem cell transplant (HSCT) procedures for all indications. It also stores immunosuppressive treatments for bone marrow failure syndromes (i.e. aplastic anaemias), cell therapy treatments other than HSCT and donor information pertaining to collection and donor follow up.

All EBMT centers are asked to submit the minimum essential data as recorded through the EBMT Cellular and Gene Therapy Form. Centers are instructed to electronically submit the first registration on the day of treatment (Day 0) or within a week of Day 0. An update should be submitted 100 days, and 6 months after the date of transplant or cell therapy infusion for non-transplanted patients, or when the patient dies, whichever comes first. Yearly follow up data should be submitted for all patients from then onwards.

7.5. Study Size

Within 4 years, Kite projects 400 patients are to have been treated with commercial Tecartus in Europe and it is anticipated that approximately 50% (200) of those patients will consent to the documentation of their data in the EBMT Registry. Based on the gender distribution in MCL, it is expected that approximately 50 female and 150 male patients will be documented at this time point. These first 200 eligible patients who have been treated with Tecartus and documented in the EBMT Registry will be evaluated in the effectiveness part of this study.

A sample size of 200 patients will allow to estimate an ORR and the according 95% confidence interval as tabulated in Table 7:

Table 7. 95% Confidence Interval of ORR by the Assumption of Observed ORR in 200 Patients

Assumed observed ORR based on 200 patients	Lower Limit of 95% CI[b]	Upper Limit of 95% CI[b]
97% (194 out of 200)	94%	99%
93% (186 out of 200)[a]	89%	96%
90% (180 out of 200)	85%	94%
85% (170 out of 200)	79%	90%
80% (160 out of 200)	74%	85%
75% (150 out of 200)	68%	81%

a 93% is the observed ORR in the ZUMA-2 study {Wang 2020}"
b 95% CI is calculated based on Clopper-Pearson exact method

For the safety part this study plans to evaluate all eligible patients who have been treated with Tecartus and documented in the EBMT Registry within 5 years from study start. In addition to the further characterization of the immediate and established toxicities of Tecartus, the study will evaluate rare and delayed safety events that occur in patients during 15 person-years of follow up. In that 5-year period, Kite projects 700 patients are to have been treated with commercial Tecartus in Europe and it is anticipated that approximately 50% (350) of those patients will consent to the documentation of their data in the EBMT Registry. The available person-years of follow-up are approximated using a piecewise linear survival curve with 2-year survival rate of 65% (assumption based on the primary analysis of ZUMA-2) and an assumption of long term 15-year survival rate of 35%, indicating an average person-years of follow-up of 8.15 years. Kite also assumes 10% overall loss to follow up, resulting in total person-years of follow-up of approximately 2567. This number of person-years of follow-up will provide 97%, or 82%, or 68%, or 58%, or 50% likelihood of seeing at least one event of interest, if the true rate per 15 years of exposure is at least 1:50, or 1:100, or 1:150, or 1:200, or 1:250, respectively. The number of 350 patients used for calculation is an assumption. The true study size for the safety part of this study will be the actual number of patients documented in the EBMT Registry within 5 years from study start.

7.6. Data Management

Data will be entered into the EBMT Registry by the centers utilizing the EBMT Cellular and Gene Therapy Form. EBMT will liaise with individual centers and will provide standard training on how to enter the data and how to use the data management system. Trained personnel will enter data directly into the EBMT Registry database, users will have user accounts with password in order to gain access to the EBMT Registry database. EBMT will cooperate with centers to reduce the amount of missing/erroneous data in the registry.

An imperative need for clear understanding of the secondary nature of the data is appreciated, wherein data are transcribed into the EBMT Registry from the medical record. To fully ensure the secondary categorization of the data is not disrupted, personnel at the centers will be trained

and instructed by the EBMT to enter only information available in the medical record, and to make no inferences outside of this practice.

Data will be collected at the center's standard follow up time points, including at least time points during the first year at approximately Day 100, 6 and 12 months and then annually thereafter. Expedited reporting of individual case safety reports to EBMT or by EBMT will not occur. Reporting of adverse events by centers or clinicians will follow the standard spontaneous reporting system per local regulations and timelines as described in Section 9.

The center that administers Tecartus is responsible for reporting follow-up unless the responsibilities are formally transferred to and accepted by a healthcare provider at another center. Patients who receive a hematopoietic cell transplantation (HCT) or other cellular therapy or any other treatment for the primary disease after Tecartus will continue to be followed.

EBMT will conduct the study specific analyses and provide overviews to update Kite Inc. regarding the progress of the data entry into the EBMT Registry. Reports will be jointly prepared as described in Section 10.1.

7.6.1. Data Transfer Procedure

EBMT will provide raw data outputs in a standard format to Kite, and these full datasets will be provided annually.

7.7. Data Analysis

7.7.1. Primary Endpoint and Effectiveness Endpoints

7.7.1.1. Primary Endpoint

- Overall response rate

7.7.1.2. Effectiveness Endpoints

- Complete remission rate
- Time to relapse or progression of the primary disease: time to relapse or progression is defined as the time from Tecartus infusion to the first relapse or progression or significant worsening of the primary disease (MCL), or death due to relapse or progression of the primary disease. Non-primary disease related mortality will be taken as a competing risk. Relapse of the primary disease is defined as reappearance of the primary tumor among patients who achieved a remission as the best response. Progression of the primary disease is defined by at least a 50% increase in the size of an existent mass or lymph node or increase in the number of lymph nodes or new sites of disease. Refer to the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma {Cheson 2007} and Lugano Classification {Cheson 2014} for more details.

- Duration of response: duration of response is defined as the time from the date of the first documented response (CR or PR) to the date of the first documented progression, or first documented relapse, or death due to primary disease, whichever happens first. DOR is determined only among patients who achieve a CR or PR after the first infusion of Tecartus.

- Time to next treatment of the primary disease: time from Tecartus infusion to next treatment of the primary disease (MCL) or death due to relapse or progression of the primary disease. Non-primary disease related mortality will be taken as a competing risk.

- Effectiveness endpoints by gender and age

- Effectiveness endpoints in special populations (patients with prior stem cell transplantation, high-risk r/r MCL patients per Mantle Cell Lymphoma International Prognostic Index [MIPI] score, CD19 expression status).

7.7.2. Safety Endpoints

- Overall survival: overall survival is the time from the date of Tecartus infusion to the date of death due to any reason.

- Incidence rates, time to onset, type and location of secondary malignancy

- Incidence rates, severity, time to onset, management and resolution of CRS

- Incidence rates, severity, time to onset, management and resolution, and type of neurologic events

- Incidence rates of prolonged cytopenias and time to recovery of ANC and platelets

- Incidence rates, type, organism, resolution, and time to onset of serious infections

- Incidence rates, time to onset of hypogammaglobulinemia, and use of replacement immunoglobulin therapy

- Safety and effectiveness endpoints on subgroups by gender, age, and in special populations (patients with prior allogeneic SCT, high-risk comorbidity index, patients treated with OOS product), and additional subgroups may also be explored

- Incidence rate, severity, resolution, and time to onset of TLS

- Incidence rate, resolution, time to onset of aggravated GvHD by acute and chronic type; incidence rate, severity and relationship to cell therapy for acute GvHD

- Frequency of detection of RCR in samples of patients with secondary malignancies

Time to onset of event of interest (secondary malignancy, or CRS, or neurologic events, or serious infections, or hypogammaglobulinemia) is defined as the time from the first Tecartus

infusion to the date of onset of the first event of interest, i.e., the date of the first onset of the event or censoring – the date of the first Tecartus infusion + 1. Deaths before experiencing the event will be taken as a competing risk.

7.7.3. Other Exploratory Endpoints

- Occurrence of loss of target antigen in patients relapsing after Tecartus therapy
- Occurrence of functional CAR-T persistence in patients relapsing after Tecartus therapy
- Occurrence of pregnancy, and pregnancy outcome among women with childbearing potential

7.7.4. General Considerations for Data Analysis

The study will make secondary use of the data available in the EBMT Registry. Analysis of all endpoints for this study will include all patients who satisfy the eligibility criteria, are documented within the EBMT Registry, and are treated with Tecartus.

Categorical variables will be summarized descriptively by number and percentage of patients in each categorical definition and will include 95% confidence intervals (CIs). Continuous variables will be summarized descriptively by mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum.

This study will evaluate the risk of age, gender, and special populations (patients with prior allogeneic SCT, high-risk comorbidity index, patients treated with OOS product) on the effectiveness and safety endpoints using multivariable regression analyses. Depending on the data, additional baseline characteristics may also be explored.

Patient incidence of endpoint events will be provided. Multivariate Poisson regression analyses will be used to estimate cumulative incidence rates adjusted for follow-up period and specified characteristics (as mentioned in the prior paragraph) to estimate their prognostic effect on the outcome.

Kaplan-Meier curves will be used to illustrate all time-to-event data. Competing risk analysis method will be used for the analysis of time to onset and duration of endpoint events, time to relapse or progression of primary disease and time to next treatment of primary disease, and the cumulative incidence at specified time points will be provided. Cox-proportional Hazard models will be used to model multivariate time-to-event data adjusted for specified characteristics (as mentioned in the prior paragraph) to estimate their prognostic effect on the outcome.

For the effectiveness part the analysis of the effectiveness endpoints will be conducted when effectiveness data from approximately 200 eligible patients were documented. Time to event endpoints will be analyzed through Kaplan-Meier method (median, 1st quartile, 3rd quartile along with their 95% confidence interval will be provided if applicable). Cumulative incidence for relapse or progression of primary disease will also be provided through competing risk method.

The potential impact of the missing values on the analysis will be evaluated and possible patterns of relationship between missing values and both influential characteristics and outcomes will be investigated. Results of the analysis of the type of missing data will be described in the results to support the appropriateness of the statistical analysis performed.

Missing events due to deaths will be adjusted through competing risk analysis method for time to-event subjects described above and in Section 7.7.5 and 7.7.6. The extent of missing data in the study will be described and tabulated. When possible the number of missing data will be reduced by retrieving the data or imputing the correct value if it can be derived from other information already collected in this protocol. Imputation methods will be used to account for missing values in the dataset for those variables used in multivariate modeling (demographics, baseline disease assessment, medical history, treatment history) following the current ENCePP guidelines {Pharmocovigilance 2018}, {Rubin 1987}, {Moons 2006}, {Wlelch 2014}. Multiple imputation by chained equations (MICE) as sequential regression multiple imputation will be used handling of missing data {Azur 2011}. Using MICE, missing values are imputed based on the observed values for a given individual and the relationships within the data for other participants. The imputation methods will not be applied when the percentage of missing is significant (>40%), or the assumption of the imputation methods is not hold.

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by Preferred Term (PT) and primary System Organ Class (SOC).

Published literature and relevant databases will be reviewed during the five years from start of data collection to identify a suitable comparator. If an appropriate comparator is forthcoming a meta-analysis or a patient level data specific analysis to compare the effectiveness and safety between Tecartus and the selected comparator will be conducted, subject to data availability.

7.7.5. Analysis of Primary Endpoint and Effectiveness Endpoints

7.7.5.1. Analysis of Primary Endpoint

Overall response rate: The subject incidence of best overall response (BOR) including Complete remission / Normalisation of organ function / No infection present (CR), Partial remission / Partial or non normalisation of organ function (PR), no response (NR), disease progression or worsening of organ function (PD), or not evaluated will be tabulated. The objective response rate (ORR) defined as the incidence of CR or PR will be calculated. The 95% confidence intervals will be provided for ORR using exact bionomial methods.

7.7.5.2. Analysis of Effectiveness Endpoints

Complete remission rate: Complete remission rate is defined as the incidence of CR. The 95% confidence intervals will be provided using exact binomial methods.

Duration of response: The cumulative incidence of DOR and 95% CIs will be estimated using the competing risk analysis method, with death due to reasons other than primary disease considered as a competing event.

Time to next treatment of the primary disease: The cumulative incidence of time to next treatment and 95% CI will be estimated using competing risk analysis method, with death without relapse or progression or without subsequent treatment of primary disease considered as a competing risk. Pointwise estimates and 95% CIs at 6, 12, 24, and 36 months will be calculated.

Time to relapse or progression of the primary disease: The cumulative incidence of relapse or disease progression and 95% CI will be estimated using competing risk analysis method, with death without relapse or progression considered as a competing risk. Pointwise estimates and 95% CIs at 6, 12, 24, and 36 months will be calculated.

ORR, CRR and DOR, as well as the time to next treatment, relapse or progression of the primary disease will be analyzed on the subgroups of gender, age, and in special population (patients with prior allogeneic stem cell transplantation [SCT], high-risk r/r MCL patients per Mantle Cell Lymphoma International Prognostic Index [MIPI] score, CD19 expression status).

Missing data in effectiveness variables will be treated as non-responders. However, this will also depend on the reason of missing data. For example, if a patient did not sign the informed consent this patient will not be considered as non-responder. In case the patient's data will be excluded clarification for exclusion will be provided.

7.7.6. Analysis of Safety Endpoints

Overall survival: Overall survival (OS) is the time from date of the first Tecartus infusion to the date of death due to any reason. All patients will be followed up for survival information regardless of whether they received additional treatment post infusion. Patients who are alive at last contact will be censored at that time, but no censoring will be done for additional treatment. OS will be summarized using the Kaplan-Meier (KM) estimate. The median OS along with 95% CIs will be presented if appropriate. Causes of death will also be reported.

Secondary malignancy: The overall incidence of secondary malignancies, and secondary malignancy by type and location will be summarized using frequencies and percentages, as well as follow-up adjusted rates. Cumulative incidence curve of time to onset of secondary malignancy shown out to 15 years, treating death prior to secondary malignancy as a competing event. Estimates and 95% CIs for the cumulative incidence of secondary malignancy will be provided at 1, 2, 5, 10, and 15 years.

CRS: The overall incidence and grade of CRS will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of CRS and 95% CI will also be estimated using competing risk analysis method, with death before experiencing CRS treated as a competing event for the onset of CRS up through 30 days after Tecartus infusion. Management and resolution of CRS will also be described.

Neurologic events: The overall incidence and grade of neurologic events, both overall and by type, will be described using frequencies and percentages, as well as follow-up adjusted rates. The incidence of neurologic events and 95% CI will also be estimated using competing risk analysis method, with death before experiencing neurologic events treated as a competing event

for the onset of neurologic event up through 90 days after Tecartus infusion. Treatment and resolution of neurologic toxicities will be described.

Prolonged cytopenias: The proportion of patients who fail to recover ANC and platelet counts, as previously specified, by Day 30 after the administration of Tecartus will be described along with 95% CI using exact binomial methods. Time to event analysis for absolute neutrophil and platelets recovery will be carried out by completing risk analysis treating death without recovery of ANC or platelets as competing risk. The point estimate and 95% CI of cumulative incidence will be reported accordingly.

Serious infections: The incidence of serious infections, type and organism will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of serious infections after Tecartus infusion and 95% CI will be estimated using competing risk analysis method, with death before experiencing serious infections treated as a competing event.

Hypogammaglobulinemia: The incidence of hypogammaglobulinemia will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of hypogammaglobulinemia after Tecartus infusion and 95% CI will be estimated using competing risk analysis method, with death before experiencing hypogammaglobulinemia treated as a competing event for the onset of hypogammaglobulinemia. Use of replacement immunoglobulin therapy will also be described as part of this endpoint.

The above endpoints, together with ORR, CRR and DOR, will be analyzed on the subgroups of by gender, age, and in special populations (high-risk comorbidity index, patients treated with OOS product), and additional subgroups may also be explored.

TLS: The overall incidence and grade of TLS will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of TLS after Tecartus infusion and 95% CI will be estimated using competing risk analysis.

Aggravated GvHD: The overall incidence of GvHD, both overall and by type, will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of GvHD after Tecartus infusion and 95% CI will be estimated using competing risk analysis. The severity and relationship to Tecartus will also be summarized.

RCR: The detection of RCR in samples of patients with secondary malignancies will be described using frequencies and percentages.

7.7.7. Analysis of Other Exploratory Endpoints

Loss of target antigen: Occurrence of loss of target antigen in patients relapsing after Tecartus therapy will be described using frequencies and percentages.

Functional CAR-T persistence: Occurrence of functional CAR-T persistence in patients relapsing after Tecartus therapy will be described using frequencies and percentages.

Pregnancy and pregnancy outcome: Both the proportion of women who become pregnant and the pregnancy outcome and the newborn's health will be described as part of this outcome.

7.7.8. Interim Analysis

For the effectiveness part annual reports will be prepared for the first three years, in which an analysis of treated patients for the primary and the effectiveness endpoints will be included. For the safety part annual reports will be prepared for the first five years and then every two years, in which an analysis of treated patients for the safety endpoints will be included. The study objectives are not associated with formal hypothesis testing and no overall type I error control. These interim analyses are administrative interim analyses for the purpose of monitoring the progress of the study enrollment, safety and effectiveness profile of Tecartus.

7.8. Quality Control

The data collected will be entered in the EBMT database according to standard operating procedures, work instructions, manuals and guidelines that are in place and maintained by EBMT.

At a registry level EBMT has built in more than four thousand control triggers, which promote consistency of the data. In addition, EBMT personnel and registry users can run data quality reports, which predominantly focus on missing data. For all studies (both retrospective and prospective) based on registry data additional data cleaning efforts, including the analyses of outliers, additional data requests and if needed statistic adjustments for missing data, are performed.

Apart from remote monitoring activities, on-site monitoring of data for 10% of the included Tecartus patients will be performed by the EBMT. Centers will be selected for on-site monitoring based on a risk-based approach using quality indicators as described in the monitoring plan.

Additional quality control measures supported by EBMT include:

- Automatic data validation checks verify the accuracy and internal consistency of entries in the database at the point of entry.

- Data quality control reports can be run by users (or by registry personnel) to check for missing, inconsistent or incorrect data.

- Follow-up requests on missing or incorrect data are issued by the registry/Study Office, this also applies, if yearly follow up data were not submitted for a patient during the up to 15 year follow-up period.

- Education and training sessions (face to face and on-line) are available for data entry staff.

- Remote manual data quality review is performed in accordance with the study data quality and monitoring documents. In addition, monitors will engage centers with regard to data

quality and completeness via telephone calls and may perform onsite visits, as documented in the EBMT monitoring plan.

7.9. Limitations of the Research Methods

The EBMT Registry allows patient data entry any time after Tecartus infusion; therefore this study has the characteristic disadvantages of retrospective studies, and these include, information bias, history bias and recall bias. However, there will be an effort to encourage patient documentation in the EBMT Registry as promptly as possible to capture data continuously going forward. The EBMT monitoring plan further states that the site is responsible for completing the data collection forms within 6 weeks after a patient visit.

Information bias can be prevented by using standard measurement instruments, such as the electronic data collection form and appropriate training of personnel entering the data. Appropriate training of personnel entering data is also important to avoid missing values when checking the patients' medical records.

7.10. Other Aspects

7.10.1. Study Discontinuation

No patient's treatment will be dictated by the protocol of this long-term observational study or by EBMT, or Kite. Consequently, continuing or discontinuing this study will not impact patient care. Therefore, identification of adverse effects of Tecartus will not constitute sufficient reason to terminate the study. However, early termination of the study will be considered if:

- Sufficient information is accumulated to meet the scientific objectives of the study
- The feasibility of collecting sufficient information is reduced to unacceptable levels because of low exposure rates, extremely slow patient accrual, or loss of the ability to follow-up

In case such conditions are met, any consideration for termination of the study will be discussed and agreed with the European Medicines Agency (EMA) beforehand.

8. PROTECTION OF HUMAN SUBJECTS

Because this is a non-interventional study with no pre-specified interventions and no interaction with patients, no potential physical or psychological risks to patients exist. This study will make secondary use of data collected within the EBMT Registry to capture information about Tecartus.

EBMT will use standard processes for ensuring the protection of human subjects for patients whose cellular therapy data are reported to the EBMT Registry. Participating centers are responsible for obtaining informed consent for patient data entry into the EBMT Registry, registering patients, and submitting baseline and follow-up data on participating patients into the EBMT Registry following EBMT's procedures and requirements.

There is no potential benefit to those who agree to have their data entered into the EBMT Registry. All benefits of long-term follow-up data collection will assist in understanding late effects that occur after treatment with CAR T cells, and thus may benefit future patients. The only risk to patients is the risk of loss of privacy and confidentiality. This is a well-mitigated risk with respect to the potential benefit of knowledge gained through these research studies.

8.1. Good Pharmacoepidemiology and Pharmacovigilance Practices

The study will be conducted in accordance with the European Medicines Agency – Guideline on Good Pharmacovigilance Practices (GVP), following the requirements for studies making secondary use of data, and including the archiving of essential documents. The study will further be conducted in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), by enclosing the ENCePP Checklist in the submission and registering the study in the EU PAS Registry.

8.2. Informed Consent

No specific informed consent will be obtained to participate in this study, as this study will involve secondary analysis of data already existing in the EBMT Registry. According to established practices of the EBMT and country requirements, at each of the centers an informed consent document will be obtained from each participating patient and maintained at the center. With this informed consent document patients will provide consenting for input of their data into the EBMT Registry.

8.3. Confidentiality

All data evaluated for this study will be collected in an EBMT data collection form with a unique identifier for each patient by each participating center. The patient identifiers will be removed and the data will contain no patient identifiable fields when analyzed data is shared with Kite by the EBMT.

9. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

The operational model for this post-authorization study protocol qualifies as non-interventional research with a design based on secondary use of data (i.e. utilizing data from patient's medical records that was previously collected for another purpose and included into the EBMT Registry data set; and where the adverse events have already occurred and will not be reported in expedited manner) as outlined in GVP Module VI. According to this guidance, reporting of safety information in the form of individual case safety reports is not required and all adverse event and safety data are only required to be recorded and summarized in the interim safety analysis and in the final study report. All adverse events will be summarized in aggregate during all reporting efforts, including in the interim and final study reports.

Reporting of individual adverse events and adverse reactions will follow the standard spontaneous reporting system per local regulations and timelines. The centers will report any suspected adverse reactions directly to Kite or respective health authorities. The SmPC and packaging materials provide respective details and contact information. Kite further provides clear guidance to HCPs in the aRMMs of the need and importance to spontaneously report and that this is not substituted by reporting into the EBMT Registry.

9.1. Kite Reporting Requirements to Regulatory Authorities

Kite is responsible for analyzing spontaneous reports of all safety information received independently from this study and for reporting to regulatory agencies as determined by country-specific legislation or regulations.

9.2. Definitions

9.2.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and should be reported.

- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)

- Any medical condition or clinically significant laboratory abnormality with an onset date before the Tecartus treatment cycle was initiated. These are considered to be preexisting conditions and should be documented on the medical history CRF (if applicable).

9.2.2. Adverse Events of Special Interest

An Adverse Events of Special Interest (AESI) for this study is considered to be an event in the focus of the safety objectives: secondary malignancies, CRS, neurologic events, serious infections, prolonged cytopenia, hypogammaglobulinemia, TLS and aggravated GvHD.

9.2.3. Adverse Drug Reactions

An adverse drug reaction (ADR) is defined as an untoward medical occurrence (unintended or noxious responses) considered causally related to an investigational or approved medicinal product at any dose administered. Adverse reactions may arise from medication errors, uses outside what is foreseen in the protocol or prescribing information (off-label use), misuse and abuse of the product, overdose, or occupational exposure.

9.2.4. Serious Adverse Events

A serious adverse event (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life -threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

9.2.5. Serious Adverse Drug Reaction

A serious adverse drug reaction (SADR) is defined as any SAE that is considered causally related to the medicinal product at any dose administered.

9.2.6. Special Situations Reports

This study has a primary endpoint to investigate pregnancy outcomes in female patients of childbearing potential reported to Kite. Other Special situation reports (SSRs) are not within the objectives of the study, but if reported spontaneously, Kite will accept these reports and handle them as appropriate.

Special situation reports include reports of abuse, drug interactions, counterfeit or falsified medicine, exposure via breastfeeding, lack of effect, medication error, misuse, occupational exposure, off-label use, overdose, pregnancy, product complaints, transmission of infectious agents via the product, and unexpected benefit. Definitions are provided below.

- Abuse: Persistent or sporadic intentional excessive use of a medicinal product by a patient.
- Drug interactions: Any reports of drug/drug, drug/food, or drug/device interactions.
- Counterfeit or falsified medicine: Any medicinal product with a false representation of a) its identity, b) its source, or c) its history.
- Exposure via breastfeeding: Reports of any exposure to a medicinal product during breastfeeding.
- Lack of effect: A report of a situation where there is apparent failure of the medicinal product or medical technology to bring about the intended beneficial effect on individuals in a defined population with a given medical problem, under ideal conditions of use.
- Medication error: Any unintentional error in the prescribing, dispensing, preparation for administration or administration of a medicinal product while the medication is in the control of a healthcare professional, patient or consumer.
- Misuse: Use of a medicinal product that is intentional and inappropriate not in accordance with its authorized product information.
- Occupational exposure: Exposure to a medicinal product as a result of one's professional or non-professional occupation.
- Off-label use: Where a medicinal product is intentionally used by a Health Care Professional for a medical purpose not in accordance with the authorized product information with respect to indication, dose, route of administration, or patient population.
- Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose in the product labelling.

- Pregnancy reports (maternal pregnancy and partner pregnancy): Reports of pregnancy following maternal or paternal exposure to the product.

- Product complaint: Complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

- Unexpected benefits: An unintended therapeutic effect where the results are judged to be desirable and beneficial.

- Transmission of infectious agents via the product: Any suspected transmission of an infected agent through a Kite medicinal product.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Kite will include updates on the progress of the study as well as updates on the published literature and relevant databases to identify a suitable comparator in the PSURs at appropriate intervals.

10.1. Study Report and Publications

10.1.1. Safety Data Reports

After start of data collection, EBMT will provide Kite with a quarterly raw data output. Based on the data transferred, Kite performs an aggregate data analysis for Tecartus within 30 days (45 days for the first report). Two quarterly reports will be submitted as appendices to the periodic safety update report (PSUR) to the Pharmacovigilance Risk Assessment Committee (PRAC). In case an intervening quarterly report identifies a major new safety finding, the respective report will be submitted promptly as stand-alone document. Particular attention will be paid to Adverse Events of Special Interest (AESIs) – which are considered to be the events which are the focus of the safety objectives (please see below and in Section 9.2.2) – where information is available for patient level presentation and causality assessment, this will be included.

The safety data reports will contain the following information, as available:

- Patient enrollment in registry
- Baseline characteristics
- Aggregate numbers of reported fatal adverse events
- Aggregate numbers of all reported adverse events
- Review of events considered AESIs via the safety objectives of this study: secondary malignancies, CRS, neurologic events, serious infections, prolonged cytopenia, hypogammaglobulinemia, TLS and aggravated GvHD
- If reported, review of any unexpected events, which do not fall under the previously recognized risks or ADRs of special interest
- Summary and conclusions

10.1.2. Annual Reports

For the effectiveness part annual reports will be prepared for the first 3 years, in which an analysis of treated patients for the primary and the effectiveness endpoints will be included. For the safety part annual reports will be prepared for the first 5 years and then every 2 years thereafter, in which an analysis of treated patients for the safety endpoints will be included. The

EBMT Cellular and Gene Therapy Form is under the control of the EBMT and its content can change throughout the course of the study (see 7.2).

Based upon the approved reports, Kite will submit information to regulatory agencies in accordance with any agreements/commitments.

10.1.3. Final Report

Following the final data analysis, Kite and EBMT will cooperate to prepare an appropriate final report, which will be submitted to the Regulatory authorities as applicable by Kite as the study sponsor.

10.1.4. Publications, Conference Abstracts, and Manuscripts

All proposed publications and conference presentations arising from the study will be reviewed by Kite and EBMT representatives prior to submission. Both EBMT and Kite will share responsibilities in the development of the statistical analysis plan, data analysis, abstracts and manuscripts. The EBMT investigators and Kite staff may share authorship. The study contract between EBMT and Kite will outline the requirements for publication.

Kite shall communicate the final manuscript to the EMA and the competent authorities of the Member States in which the product is authorized within 2 weeks after first acceptance for publication.

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12. ANNEXES

Annex 1. List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
1	None		

Annex 2. ENCePP Checklist for Study Protocols

Study title:
LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF TECARTUS FOR TREATMENT OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA (MCL)

EU PAS Register® number: tbd
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	4, 7
2.1.2 The objective(s) of the study?	☒	☐	☐	4, 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	4, 9
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	4, 9
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.6
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	9
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	4, 9
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	4, 9
	4.2.2 Age and sex	☐	☒	☐	
	4.2.3 Country of origin	☐	☒	☐	
	4.2.4 Disease/indication	☒	☐	☐	4, 9
	4.2.5 Duration of follow-up	☒	☐	☐	4, 9
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	4, 9

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	9.7
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	9.7
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	4, 8, 9
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	4, 9
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	4, 9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☒	☐	9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	4, 9

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	4, 9
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	4, 9
9.1.3 Covariates and other characteristics?	☒	☐	☐	4, 9
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	4, 9

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	4, 9
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	4, 9
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	9.7
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9
9.3.3 Covariates and other characteristics?	☐	☒	☐	9
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	10

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	4, 9
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	4, 9
10.3 Are descriptive analyses included?	☒	☐	☐	4, 9
10.4 Are stratified analyses included?	☐	☒	☐	9
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	9
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	9

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☒	☐	
12.1.2 Information bias?	☒	☐	☐	9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	9

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☐	☐	☒	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Heribert Ramroth

Date: November 18, 2021 | 6:56:40 AM PST

Signature: DocuSigned by: 2DA6CC5FF4C340B...

Annex 3. Reference Safety Information

Current version of the EU SmPC for Tecartus®.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Tecartus (autologous anti-CD19-transduced CD3+ cells) is a gene therapy medicinal product containing autologous T cells genetically modified *ex vivo* using a retroviral vector encoding an anti-CD19 chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 co-stimulatory domain and CD3-zeta signalling domain.

2.2 Qualitative and quantitative composition

Each patient specific single infusion bag contains a dispersion of anti-CD19 CAR T cells in approximately 68 mL for 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.

Excipient(s) with known effect

This medicinal product contains 300 mg sodium.
Each dose contains 0.05 mL of dimethyl sulfoxide (DMSO) per mL of Tecartus.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion.

A clear to opaque, white to red dispersion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tecartus is indicated 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.

4.2 Posology and method of administration

Tecartus must be administered in a qualified treatment centre by a physician with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Tecartus. At least 1 dose of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion. The qualified treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose.

Patients are expected to enrol in a registry and will be followed in the registry in order to better understand the long-term safety and efficacy of Tecartus.

Posology

Tecartus is intended for autologous use only (see section 4.4).

A single dose of Tecartus contains 2×10^6 CAR-positive viable T cells per kg of body weight (range: 1×10^6–2×10^6 cells/kg), or maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above in approximately 68 mL dispersion in an infusion bag.

Tecartus is recommended to be infused 3 to 14 days after completion of the lymphodepleting chemotherapy. The availability of the treatment must be confirmed prior to starting the lymphodepleting regimen.

Pre-treatment (lymphodepleting chemotherapy)

- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m² and fludarabine 30 mg/m² should be administered intravenously on the 5th, 4th, and 3rd day before infusion of Tecartus.

Pre-medication

- To minimise potential acute infusion reactions, it is recommended that patients be pre-medicated with paracetamol 500 to 1,000 mg given orally and diphenhydramine 12.5 to 25 mg intravenous or oral (or equivalent) approximately 1 hour prior to infusion.
- Prophylactic use of systemic corticosteroids is not recommended (see section 4.5).

Monitoring after infusion

- Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurologic events.
- After the first 10 days following the infusion, the patient should be monitored at the physician's discretion.
- Patients should be instructed to remain within proximity (within 2 hours of travel) of a qualified treatment centre for at least 4 weeks following infusion.

Special populations

Elderly

No dose adjustment is required in patients ≥65 years of age.

Patients seropositive for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV)

There is no experience with manufacturing Tecartus for patients with a positive test for HIV, active HBV, or active HCV infection. Therefore, the benefit/risk has not yet been established in this population.

Paediatric population

The safety and efficacy of Tecartus in children and adolescents aged less than 18 years have not yet been established. No data are available.

Method of administration

Tecartus is for intravenous use only.

Tecartus must not be irradiated. Do NOT use a leukodepleting filter.

Precautions to be taken before handling or administering the medicinal product
This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Tecartus should take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases (see section 6.6).

Preparation for infusion
- Verify that the patient's identity (ID) matches the patient identifiers on the Tecartus metal cassette.
- The Tecartus infusion bag must not be removed from the metal cassette if the information on the patient-specific label does not match the intended patient.
- Once the patient ID is confirmed, remove the infusion bag from the metal cassette.
- Check that the patient information on the metal cassette label matches that on the bag label.
- Inspect the infusion bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines for handling of waste of human-derived material (or immediately contact Kite).
- Place the infusion bag inside a second bag.
- Thaw Tecartus at approximately 37 °C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Tecartus should not be washed, spun down, and/or re-suspended in new media prior to infusion. Thawing should take approximately 3 to 5 minutes.
- Once thawed, Tecartus is stable at room temperature (20 °C – 25 °C) for up to 3 hours. However, Tecartus infusion should begin within 30 minutes of thaw completion.

Administration
- For autologous single use only.
- Tocilizumab and emergency equipment should be available prior to infusion and during the monitoring period.
- A leukodepleting filter must not be used.
- Central venous access is recommended for the administration.
- Verify the patient ID again to match the patient identifiers on the Tecartus bag.
- Prime the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) prior to infusion.
- Infuse the entire content of the Tecartus bag within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the bag during infusion to prevent cell clumping.
- After the entire content of the bag is infused, rinse the tubing at the same infusion rate with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) to ensure all the treatment is delivered.

For instructions on the handling, accidental exposure to and disposal of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Contraindications of the lymphodepleting chemotherapy must be considered.

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient should be kept for a period of 30 years.

General

Warnings and precautions of lymphodepleting chemotherapy must be considered.

Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurologic events. After the first 10 days following infusion, the patient should be monitored at the physician's discretion.

Counsel patients to remain within the proximity of a qualified treatment centre for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS or neurological adverse reactions occur. Monitoring of vital signs and organ functions should be considered depending on the severity of the reaction.

Reasons to delay treatment

Due to the risks associated with Tecartus treatment, infusion should be delayed if a patient has any of the following conditions:

- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions, or hypotension) including from preceding chemotherapies.
- Active uncontrolled infection or inflammatory disease.
- Active graft-versus-host disease (GvHD).

In some cases, the treatment may be delayed after administration of the lymphodepleting chemotherapy regimen. If the infusion is delayed for more than 2 weeks after the patient has received the lymphodepleting chemotherapy, lymphodepleting chemotherapy regimen should be administered again (see section 4.2)

Serological testing

Screening for HBV, HCV, and HIV should be performed before collection of cells for manufacturing of Tecartus (see section 4.2).

Blood, organ, tissue and cell donation

Patients treated with Tecartus should not donate blood, organs, tissues, or cells for transplantation.

Active central nervous system (CNS) lymphoma

There is no experience of use of this medicinal product in patients with active CNS lymphoma defined as detectable cerebrospinal fluid malignant cells or brain metastases confirmed by imaging. Therefore, the benefit/risk of Tecartus has not been established in this population.

Concomitant disease

Patients with a history of or active CNS disorder or inadequate renal, hepatic, pulmonary, or cardiac function were excluded from the study. These patients are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

Cytokine release syndrome

Nearly all patients experienced some degree of CRS. Severe CRS, which can be life-threatening, was very commonly observed with Tecartus with a median time to onset of 3 days (range: 1 to 13 days). Patients should be closely monitored for signs or symptoms of these events, such as high fever, hypotension, hypoxia, chills, tachycardia and headache (see section 4.8). CRS should be managed at the physician's discretion, based on the patient's clinical presentation and according to the CRS management algorithm provided in Table 1.

Diagnosis of CRS requires excluding alternate causes of systemic inflammatory response, including infection.

Management of cytokine release syndrome associated with Tecartus
At least 1 dose per patient of tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, must be on site and available for administration prior to Tecartus infusion. The qualified treatment centre should have access to an additional dose of tocilizumab within 8 hours of each previous dose.

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, as summarised in Table 1. Patients who experience Grade 2 or higher CRS (e.g. hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should 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.

CRS has been known to be associated with end organ dysfunction (e.g., hepatic, renal, cardiac, and pulmonary). In addition, worsening of underlying organ pathologies can occur in the setting of CRS. Patients with medically significant cardiac dysfunction should be managed by standards of critical care and measures such as echocardiography should be considered. In some cases, macrophage activation syndrome (MAS) and haemophagocytic lymphohistiocytosis (HLH) may occur in the setting of CRS.

Evaluation for haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) should be considered in patients with severe or unresponsive CRS.

Tecartus continues to expand and persist following administration of tocilizumab and corticosteroids. Tumour necrosis factor (TNF) antagonists are not recommended for management of Tecartus-associated CRS.

Table 1 CRS grading and management guidance

CRS Grade *(a)*	**Tocilizumab**	**Corticosteroids**
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	If not improving after 24 hours, administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg).	N/A

CRS Grade *(a)*	Tocilizumab	Corticosteroids
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO_2 or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity *(b)*.	Administer tocilizumab *(c)* 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24 hour period; maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS, or if no response to second or subsequent doses of tocilizumab, consider alternative measures for treatment of CRS. If improving, discontinue tocilizumab.	If no improvement within 24 hours after starting tocilizumab, manage as per Grade 3. If improving, taper corticosteroids, and manage as Grade 1.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours) until Grade 1, then taper corticosteroids. If improving, manage as Grade 2. If not improving, manage as Grade 4.
Grade 4 Life-threatening symptoms. Requirements for ventilator support or continuous veno-venous haemodialysis or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer methylprednisolone 1000 mg intravenously per day for 3 days. If improving, taper corticosteroids, and manage as Grade 3. If not improving, consider alternate immunosuppressants.

N/A = not available/not applicable
(a) Lee et al 2014.
(b) Refer to Table 2 for management of neurologic adverse reactions.
(c) Refer to tocilizumab summary of product characteristics for details.

Neurologic adverse reactions

Severe neurologic adverse reactions (encephalopathy, confusional state or delirium, decreased level of consciousness, seizures, aphasia), which could be life-threatening, were very commonly observed in patients treated with Tecartus with a median time to onset of 8 days (range: 1 to 262 days) (see section 4.8).

Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive-care supportive therapy for severe or life-threatening neurologic toxicities. Non-sedating, anti-seizure medicines should 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 Table 2.

Table 2 Neurologic adverse reaction grading and management guidance

Grading assessment	Concurrent CRS	No concurrent CRS
Grade 2	Administer tocilizumab as per Table 1 for management Grade 2 CRS. If not improving within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less, then taper corticosteroids. If improving, discontinue tocilizumab. If still not improving, manage as Grade 3.	Administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less. If improving, taper corticosteroids
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 3	Administer tocilizumab as per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids. If improving, discontinue tocilizumab and manage as Grade 2. If still not improving, manage as Grade 4.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids. If not improving, manage as Grade 4.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab as per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days. If improving, then manage as Grade 3. If not improving, consider alternate immunosuppressants.	Administer methylprednisolone 1000 mg intravenously per day for 3 days. If improving, then manage as Grade 3. If not improving, consider alternate immunosuppressants.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

Infections and febrile neutropenia

Severe infections, which could be life-threatening, were very commonly observed with Tecartus (see section 4.8).

Patients should be monitored for signs and symptoms of infection before, during and after infusion and treated appropriately. Prophylactic antibiotics should be administered according to standard institutional guidelines.

Febrile neutropenia has been observed in patients after Tecartus infusion (see section 4.8) and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

In immunosuppressed patients, life-threatening and fatal opportunistic infections including disseminated fungal infections and viral reactivation (e.g., HHV-6 and progressive multifocal leukoencephalopathy) have been reported. The possibility of these infections should be considered in patients with neurologic events and appropriate diagnostic evaluations should be performed.

Viral reactivation

Viral reactivation, e.g. Hepatitis B virus (HBV) reactivation, can occur in patients treated with medicinal products directed against B cells and could result in fulminant hepatitis, hepatic failure, and death.

Prolonged cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Tecartus infusion and should be managed according to standard guidelines. Grade 3 or higher prolonged cytopenias following Tecartus infusion occurred very commonly and included thrombocytopenia, neutropenia, and anaemia (see section 4.8). Patient blood counts should be monitored after Tecartus infusion.

Hypogammaglobulinaemia

B-cell aplasia leading to hypogammaglobulinaemia can occur in patients receiving treatment with Tecartus. Hypogammaglobulinaemia was very commonly observed in patients treated with Tecartus (see section 4.8). Hypogammaglobulinaemia predisposes patients to have infections. Immunoglobulin levels should be monitored after treatment with Tecartus and managed using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement in case of recurrent infections and should be taken according standard guidelines.

Hypersensitivity reactions

Serious hypersensitivity reactions including anaphylaxis, may occur due to DMSO or residual gentamicin in Tecartus.

Secondary malignancies

Patients treated with Tecartus may develop secondary malignancies. Patients should be monitored life-long for secondary malignancies. In the event that a secondary malignancy occurs, the company should be contacted to obtain instructions on patient samples to collect for testing.

Tumour lysis syndrome (TLS)

TLS, which may be severe, has occasionally been observed. To minimise risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to Tecartus infusion. Signs and symptoms of TLS should be monitored, and events managed according to standard guidelines.

Prior stem cell transplantation (GvHD)

It is not recommended that patients who underwent an allogeneic stem cell transplant and suffer from active acute or chronic GvHD receive treatment because of the potential risk of Tecartus worsening GvHD.

Prior treatment with anti-CD19 therapy

Tecartus is not recommended if the patient has relapsed with CD19-negative disease after prior anti-CD19 therapy.

Sodium content

This medicinal product contains 300 mg sodium per infusion, equivalent to 15% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Prophylactic use of systemic corticosteroids may interfere with the activity of Tecartus. Prophylactic use of systemic corticosteroids is therefore not recommended before infusion (see section 4.2).

Administration of corticosteroids as per the toxicity management guidelines does not impact the expansion and persistence of CAR T cells.

Live vaccines

The safety of immunisation with live viral vaccines during or following Tecartus treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Tecartus treatment, and until immune recovery following treatment.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

The pregnancy status of women of childbearing potential must be verified before starting Tecartus treatment.

See the prescribing information for lymphodepleting chemotherapy for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with Tecartus.

Pregnancy

There are no available data with Tecartus use in pregnant women. No reproductive and developmental toxicity animal studies have been conducted with Tecartus to assess whether it can cause foetal harm when administered to a pregnant woman (see section 5.3).

It is not known if Tecartus has the potential to be transferred to the foetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause foetal toxicity, including B-cell lymphocytopenia. Therefore, Tecartus is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised on the potential risks to the foetus. Pregnancy after Tecartus therapy should be discussed with the treating physician.

Assessment of immunoglobulin levels and B-cells in newborn infants of mothers treated with Tecartus should be considered.

Breast-feeding

It is unknown whether Tecartus is excreted in human milk or transferred to the breast-feeding child. Breast-feeding women should be advised of the potential risk to the breast-fed child.

Fertility

No clinical data on the effect of Tecartus on fertility are available. Effects on male and female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

Tecartus has major influence on the ability to drive and use machines.

Due to the potential for neurologic events, including altered mental status or seizures, patients should not drive or operate heavy or potentially dangerous machines until at least 8 weeks after infusion or until resolution of neurologic adverse reactions.

4.8 Undesirable effects

Summary of the safety profile

The safety data described in this section reflect exposure to Tecartus in ZUMA-2, a Phase 2 study in which a total of 82 patients with relapsed/refractory MCL received a single dose of CAR-positive viable T cells (2×10^6 or 0.5×10^6 anti-CD19 CAR T cells/kg) based on a recommended dose which was weight-based.

The most significant and frequently occurring adverse reactions were cytokine release syndrome (91%), infections (56%) and encephalopathy (51%).

Serious adverse reactions occurred in 57% of patients. The most common serious adverse reactions included encephalopathy (26%), infections (28%) and cytokine release syndrome (15%).

Grade 3 or higher adverse reactions were reported in 65% of patients. The most common Grade 3 or higher non-haematological adverse reactions included infections (32%) and encephalopathy (24%). The most common Grade 3 or higher haematological adverse reactions included neutropenia (99%), leukopenia (98%), lymphopenia (96%), thrombocytopenia (65%) and anaemia (56%).

Tabulated list of adverse reactions

Adverse reactions described in this section were identified in patients exposed to Tecartus in ZUMA-2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3 Adverse drug reactions identified with Tecartus

System Organ Class (SOC)	Frequency	Adverse reactions
Infections and infestations		
	Very common	Unspecified pathogen infections Viral infections Bacterial infections Fungal infections
Blood and lymphatic system disorders		
	Very common	Neutropenia[a] Lymphopenia[a] Leukopenia[a] Anaemia[a] Thrombocytopenia[a] Coagulopathy
Immune system disorders		
	Very common	Cytokine Release Syndrome[b] Hypogammaglobulinaemia
Metabolism and nutrition disorders		
	Very common	Hypophosphataemia[a] Decreased appetite
	Common	Dehydration Hypoalbuminemia[a]

System Organ Class (SOC)	Frequency	Adverse reactions
Psychiatric disorders		
	Very common	Insomnia Delirium Anxiety
Nervous system disorders		
	Very common	Encephalopathy Tremor Headache Aphasia Dizziness Neuropathy
	Common	Ataxia Seizure Increased intracranial pressure
Cardiac disorders		
	Very common	Tachycardias Bradycardias
	Common	Non-ventricular arrhythmias
Vascular disorders		
	Very common	Hypotension Hypertension Thrombosis
	Common	Haemorrhage
Respiratory, thoracic and mediastinal disorders		
	Very common	Cough Pleural effusion Dyspnoea Hypoxia
	Common	Respiratory failure Pulmonary oedema
Gastrointestinal disorders		
	Very common	Constipation Nausea Diarrhoea Oral pain Abdominal pain Vomiting Dysphagia
	Common	Dry mouth
Skin and subcutaneous tissue disorders		
	Very common	Rash
Musculoskeletal and connective tissue disorders		
	Very common	Motor dysfunction Musculoskeletal pain
Renal and urinary disorders		
	Very common	Renal insufficiency Urine output decreased
General disorders and administration site conditions		
	Very common	Fatigue Oedema Pyrexia Pain Chills
Investigations		
	Very common	Alanine aminotransferase increased[a] Aspartate aminotransferase increased[a] Hypokalaemia[a] Hyponatraemia[a] Hypocalcaemia[a] Blood uric acid increased[a]

System Organ Class (SOC)	Frequency	Adverse reactions
Only cytopenias that resulted in (i) new or worsening clinical sequelae or (ii) that required therapy or (iii) adjustment in current therapy are included in Table 3.		
[a] Frequency based on Grade 3 or higher laboratory parameter.		
[b] See section Description of selected adverse reactions.		

Description of selected adverse reactions

Cytokine release syndrome
CRS occurred in 91% of patients. Fifteen percent (15%) of patients experienced Grade 3 or higher (severe or life-threatening) CRS. The median time to onset was 3 days (range: 1 to 13 days) and the median duration was 10 days (range: 1 to 50 days). All patients (100%) recovered from CRS.

The most common signs or symptoms associated with CRS among the patients who experienced CRS included pyrexia (99%), hypotension (60%), hypoxia (37%), chills (33%), tachycardia (27%), headache (24%), fatigue (16%), nausea (13%), alanine aminotransferase increased (13%), aspartate aminotransferase increased (12%), diarrhoea (11%), and sinus tachycardia (11%). Serious adverse reactions that may be associated with CRS included hypotension, pyrexia, hypoxia, acute kidney injury, and tachycardia. See section 4.4 for monitoring and management guidance.

Neurologic events and adverse reactions
Neurologic adverse reactions occurred in 68% of patients. Thirty-three percent (33%) of patients experienced Grade 3 or higher (severe or life-threatening) adverse reactions. The median time to onset was 8 days (range: 1 to 262 days). Neurologic events resolved for 47 out of 56 patients with a median duration of 13 days (range: 1 to 567 days). Three patients had ongoing neurologic events at the time of death, including one patient with the reported event of serious encephalopathy and another patient with the reported event of serious confusional state. The remaining unresolved neurologic events were Grade 2. Eighty-five percent of all treated patients experienced the first CRS or neurological event within the first 7 days after Tecartus infusion.

The most common neurologic adverse reactions included encephalopathy (51%), tremor (38%), aphasia (20%), and delirium (18%). Serious adverse reactions including encephalopathy (26%), aphasia (6%) and seizure (2%) have been reported in patients administered with Tecartus. Serious cases of cerebral oedema which may become fatal have occurred in patients treated with Tecartus. See section 4.4 for monitoring and management guidance.

Febrile neutropenia and infections
Febrile neutropenia was observed in 6% of patients after Tecartus infusion. Infections occurred in 56% of patients in ZUMA-2. Grade 3 or higher (severe, life-threatening or fatal) infections occurred in 32% of patients including unspecified pathogen, bacterial, and viral infections in 26%, 6%, and 4% of patients respectively. See section 4.4 for monitoring and management guidance.

Prolonged cytopenias
Cytopenias are very common following prior lymphodepleting chemotherapy and Tecartus therapy.

Prolonged (present on or beyond Day 30 or with an onset at Day 30 or beyond) Grade 3 or higher cytopenias occurred in 55% of patients and included thrombocytopenia (38%), neutropenia (37%), and anaemia (17%). See section 4.4 for management guidance.

Hypogammaglobulinaemia
In ZUMA-2, hypogammaglobulinaemia occurred in 16% of patients. Grade 3 or higher hypogammaglobulinemia occurred in 1% of patients. See section 4.4 for management guidance.

Immunogenicity

The immunogenicity of Tecartus has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the

anti-CD19 CAR. To date, no anti-CD19 CAR T-cell antibody immunogenicity has been observed. Based on an initial screening assay, 17 patients tested positive for antibodies; however, a confirmatory orthogonal cell-based assay demonstrated that all 17 patients were antibody negative at all time points tested. There is no evidence that the kinetics of initial expansion, CAR T-cell function and persistence of Tecartus, or the safety or effectiveness of Tecartus, was altered in these patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There are no data regarding the signs of overdose with Tecartus.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: not yet assigned

Mechanism of action

Tecartus, a CD19-directed genetically modified autologous T-cell immunotherapy, binds to CD19 expressing cancer cells and normal B cells. Following anti-CD19 CAR T-cell engagement with CD19 expressing target cells, the CD28 co-stimulatory domain and CD3-zeta signalling domain activate downstream signalling cascades that lead to T-cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to killing of CD19-expressing cells.

Pharmacodynamic effects

In ZUMA-2, after Tecartus infusion, pharmacodynamic responses were evaluated over a 4-week interval by measuring transient elevation of cytokines, chemokines, and other molecules in blood. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF-α, interferon-gamma (IFN-γ) and IL-2 receptor alpha were analysed. Peak elevation was generally observed between 4 and 8 days after infusion and levels generally returned to baseline within 28 days.

Due to the on target, off-tumour effect of Tecartus a period of B-cell aplasia is expected following treatment.

Translational analyses performed to identify associations between cytokine levels and incidence of CRS or neurologic events showed that higher levels (peak and AUC at 1 month) of multiple serum analytes were associated with Grade 3 or higher neurologic adverse reactions and Grade 3 or higher CRS.

Clinical efficacy and safety

Relapsed or refractory MCL: ZUMA-2
The efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL who had previously received anthracycline or bendamustine-containing chemotherapy, an anti CD20 antibody, and a Bruton's tyrosine kinase inhibitor (BTKi) (ibrutinib or acalabrutinib), was evaluated in a phase 2 single-arm, open-label, multicenter trial. Eligible patients also had disease progression after last regimen or refractory disease to the most recent therapy. Patients with active or serious infections, prior allogeneic haematopoietic stem cell transplantation (HSCT), detectable cerebrospinal fluid

malignant cells or brain metastases, and any history of central nervous system lymphoma or CNS disorders were ineligible. In total, 74 patients were enrolled (*i.e.* leukapheresed) and 68 patients were treated with Tecartus. Three patients did not receive Tecartus due to manufacturing failure. Two other patients were not treated due to progressive disease (death) following leukapheresis. One patient was not treated with Tecartus after receiving lymphodepleting chemotherapy due to ongoing active atrial fibrillation. ITT was defined as all patients who underwent leukapheresis. A summary of the patient baseline characteristics is provided in Table 4.

Table 4 Summary of baseline characteristics for ZUMA-2

Category	**All leukapheresed (ITT) (N=74)**
Age (years)	
Median (min, max)	65 (38, 79)
≥ 65	58%
Male gender	84%
Median number of prior therapies (min, max)	3 (1; 5)
Relapsed/refractory subgroup	
Relapsed after auto-SCT	42%
Refractory to last MCL therapy	39%
Relapsed after last MCL therapy	19%
Patients with disease stage IV	86%
Patients with bone marrow involvement	51%
Morphological characteristic	
Classical MCL	54%
Blastoid MCL	26%
Other	1%
Unknown	19%
Received bridging therapy	
Yes	38%
No	62%
Ki-67 IHC by central laboratory	
N	49
Median	65%
Auto-SCT, autologous stem cell transplant; IHC, immunohistochemistry; Max, maximum; MCL, mantle cell lymphoma; Min, minimum;	

Tecartus was administered to patients as a single intravenous infusion at a target dose of 2×10^6 anti-CD19 CAR T cells/kg (maximum permitted dose: 2×10^8 cells) after lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously, both given on the 5th, 4th, and 3rd day before treatment. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was permitted to control disease burden.

For patients treated with Tecartus, the median time from leukapheresis to product release was 13 days (range: 9 to 20 days) and the median time from leukapheresis to Tecartus infusion was 27 days (range: 19 to 74 days, with the exception of one outlier of 134 days). The median dose was 2.0×10^6 anti-CD19 CAR T cells/kg. All patients received Tecartus infusion on day 0 and were hospitalized until day 7 at the minimum.

The primary endpoint was objective response rate (ORR) as determined by Lugano 2014 criteria by an independent review committee. Secondary endpoints included duration of response (DOR), overall survival (OS), progression free survival (PFS) and severity of adverse events.

An analysis set was defined a priori which consisted of the first 60 patients treated with Tecartus who were evaluated for response 6 months after the Week 4 disease assessment after Tecartus infusion. In this analysis set of 60 patients the ORR was 93% with a CR rate of 67%. The ORR was significantly higher than the prespecified historical control rate of 25% at a 1-sided significance level of 0.025 ($p < 0.0001$). Results in the ITT set are shown in Table 5.

Table 5 Summary of efficacy results for ZUMA-2

Category	**All leukapheresed [a](ITT) (N = 74)**
Objective response rate (ORR), n (%) [95% CI]	**62 (84%)** [73.4, 91.3]
CR n (%) [95% CI]	44 (59%) [47.4, 70.7]
PR n (%) [95% CI]	18 (24%) [15.1, 35.7]
Duration of response (DOR)[b]	
Median in months [95% CI]	NR [10.4, NE]
Range [c] in months	0.0+, 35.0+
Ongoing responses, CR+PR, CR, n (%) [d]	32 (43%), 30 (41%)
Progression free survival	
Median, months [95% CI]	16.2 [9.9, NE]
Overall survival	
Median, months [95% CI]	NR [24.6, NE]
6 month OS (%) [95% CI]	83.6 [72.9, 90.3]
12 month OS (%) [95% CI]	76.6 [65.1, 84.8]
24 month OS (%) [95% CI]	66.5 [52.8, 77.1]
Median Follow-up in months (min, max)	16.8 [7.2, 37.6]

CI, confidence interval; CR, complete remission; ITT, intent to treat; NE, not estimable; NR, not reached; OS, overall survival; PR, partial remission.

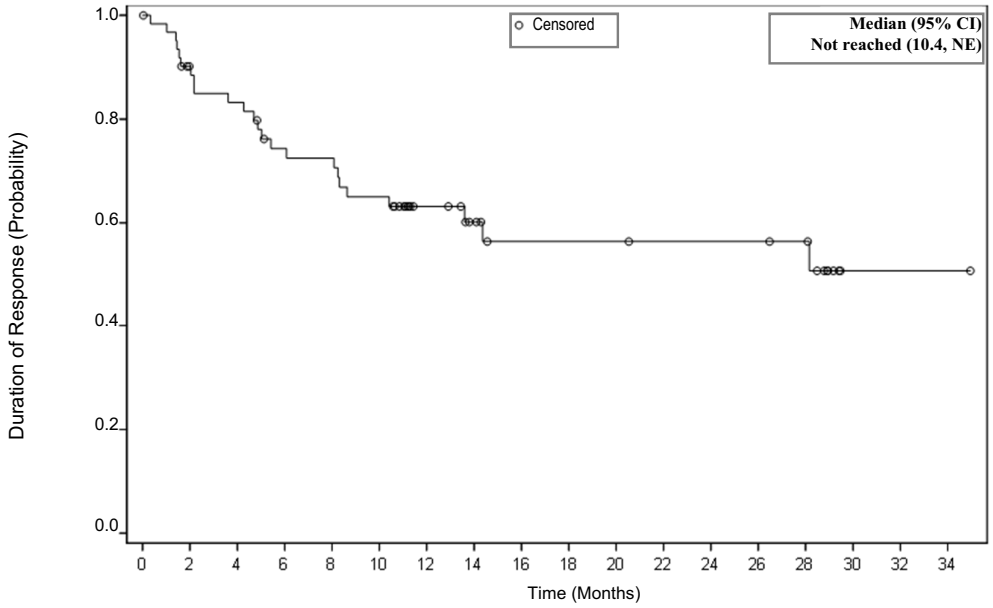
a Of the 74 patients that were enrolled (*i.e.* leukapheresed), 69 patients received lymphodepleting chemotherapy, and 68 patients received Tecartus.

b Among all responders. DOR is measured from the date of first objective response to the date of progression or death.

c A + sign indicates a censored value.

d At the data cutoff date. Percentages are calculated using the total number of patients in the analysis set as the denominator.

Figure 1 Kaplan Meier DOR in the intent to treat set



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Tecartus in all subsets of the paediatric population in treatment of mantle cell lymphoma (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme.
This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Following infusion of Tecartus, anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Peak levels of anti-CD19 CAR T cells occurred within the first 7 to 15 days after the infusion.

The number of anti-CD19 CAR T cells in blood was associated with objective response (CR or PR) (Table 6).

Table 6 Kinetic parameters of autologous anti-CD19-transduced CD3+ cells in ZUMA-2

Number of anti-CD19 CAR T cell	**Responding patients (CR or PR) (N=63)**	**Non-responding patients (N=5)**	**P-Value**
Peak (cells/µL) Median [min; max], n	97.52 [0.24, 2589.47], 62	0.39 [0.16, 22.02], 5	0.0020
AUC_{0-28} (cells/µL·days) Median [min; max], n	1386.28 [3.83 to 2.77×10^4], 62	5.51 [1.81, 293.86], 5	0.0013

P-value is calculated by Wilcoxon test

Median peak anti-CD19 CAR T-cell values were 74.08 cells/μL in patients ≥65 years of age (n=39) and 112.45 cells/μL in patients <65 years of age (n=28). Median anti-CD19 CAR T-cell AUC values were 876.48 cells/μL·day in patients ≥65 years of age and 1640.21 cells/μL·day in patients <65 years of age.

Gender had no significant impact on $AUC_{Day\ 0–28}$ and C_{max} of Tecartus.

Studies of Tecartus in patients with hepatic and renal impairment were not conducted.

5.3 Preclinical safety data

Tecartus comprises engineered human T cells; therefore, there are no representative *in vitro* assays, *ex vivo* models, or *in vivo* models that can accurately address the toxicological characteristics of the human product. Hence, traditional toxicology studies used for medicinal product development were not performed.

No carcinogenicity or genotoxicity studies have been conducted.

No studies have been conducted to evaluate the effects of this treatment on fertility, reproduction, and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cryostor CS10
Sodium chloride
Human albumin

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Tecartus is stable for 1 year when stored frozen in the vapour phase of liquid nitrogen (≤ − 150°C).

Tecartus is stable at room temperature (20 °C to 25 °C) for up to 3 hours after thawing. However, Tecartus infusion should begin within 30 minutes of thaw completion and the total infusion time should not exceed 30 min. Thawed product should not be refrozen.

6.4 Special precautions for storage

Tecartus must be stored in the vapour phase of liquid nitrogen (≤ − 150 °C) and must remain frozen until the patient is ready for treatment to ensure viable live autologous cells are available for patient administration.

For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Ethylene-vinyl acetate cryostorage bag with sealed addition tube and two available spike ports, containing approximately 68 mL of cell dispersion.

One cryostorage bag is individually packed in a shipping metal cassette.

6.6 Special precautions for disposal and other handling

Irradiation could lead to inactivation of the product.

Precautions to be taken for the transport and disposal of the medicinal product

Tecartus should be transported within the facility in closed, break-proof, leak-proof containers.

Tecartus contains genetically modified human blood cells. Local guidelines on handling of waste of human-derived material should be followed for unused medicinal products or waste material. All material that has been in contact with Tecartus (solid and liquid waste) should be handled and disposed of in accordance with local guidelines on handling of waste of human-derived material.

Accidental exposure to Tecartus must be avoided. Local guidelines on handling of human-derived material should be followed in case of accidental exposure, which may include washing of the contaminated skin and removal of contaminated clothes. Work surfaces and materials which have potentially been in contact with Tecartus must be decontaminated with appropriate disinfectant.

7. MARKETING AUTHORISATION HOLDER

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1492/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 December 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance

Kite Pharma, Inc.
2355 Utah Avenue
El Segundo
California
CA 90245
United States

Name and address of the manufacturer(s) responsible for batch release

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Key elements:

Availability of tocilizumab and site qualification

To minimise the risks associated with the treatment of Tecartus, the MAH must ensure that hospitals and their associated centres that dispense Tecartus are specially qualified in accordance with the agreed controlled distribution program.

The MAH must ensure on-site, immediate access to at least 1 dose of tocilizumab for each patient as cytokine release syndrome (CRS) management medication prior to treating patients. Hospitals and their associated centres should have access to an additional dose of tocilizumab within 8 hours of each previous dose.

Tecartus will only be supplied to hospitals and associated centres that are qualified and only if the healthcare professionals (HCP) involved in the treatment of a patient have completed the educational program.

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

HCP Educational program

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:

- provide information about the safety and efficacy long-term follow up study and the importance of contributing to such a study
- 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
- ensure that detailed instructions about the thawing procedure are provided
- before treating a patient, ensure that at least 1 dose of tocilizumab for each patient is available on site. The qualified treatment centre must have access to additional doses of tocilizumab within 8 hours

Patient Educational program

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

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to further characterise the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory Mantle cell Lymphoma (MCL) the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.	Interim reports to be submitted in accordance with the RMP. 30 June 2042

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL and the Benefit/Risk balance in the female, elderly and severely diseased patients, the MAH shall submit the results of a prospective study investigating efficacy and safety based on data from the same registry used to characterise the long-term efficacy and safety of Tecartus, according to an agreed protocol.	30 September 2025
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL the MAH shall submit the 24 months follow-up data from all treated patients in cohort 1 of the pivotal study ZUMA-2.	31 March 2022

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

METAL CASSETTE

1. NAME OF THE MEDICINAL PRODUCT

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion
autologous anti-CD19-transduced CD3+ cells (CAR+ viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous human T cells transduced with retroviral vector encoding an anti-CD19 chimeric antigen receptor (CAR) with a target dose of 2 × 10^6 anti-CD19 CAR positive viable T cells/kg.

3. LIST OF EXCIPIENTS

Excipients: Cryostor CS10, human albumin, sodium chloride.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
One sterile infusion bag.
Contents: approximately 68 mL of cell dispersion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Do not irradiate.
For intravenous use only.
Gently mix the contents of the bag while thawing.
Do NOT use a leukodepleting filter.
STOP confirm patient ID prior to infusion.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store frozen in vapour phase of liquid nitrogen ≤ − 150 °C.
Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Contains genetically-modified cells.
Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1492/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot:
Kite Patient ID:
Additional Patient ID:
Patient Name:
Patient DOB:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INFUSION BAG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion
autologous anti-CD19-transduced CD3+ cells (CAR+ viable T cells)
For intravenous use only.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot:
Kite Patient ID:
Additional Patient ID:
Patient Name:
Patient DOB:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Contents: approximately 68 mL of cell dispersion.

6. OTHER

For autologous use only.
Verify patient ID.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion
autologous anti-CD19-transduced CD3+ cells (CAR+ viable T cells)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will give you a Patient Alert Card. Read it carefully and follow the instructions on it.
- Always show the Patient Alert Card to the doctor or nurse when you see them or if you go to hospital.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tecartus is and what it is used for

Tecartus is a gene therapy medicine used for treating mantle cell lymphoma in adults. It is used when other medicines have stopped working for you (relapsed or refractory mantle cell lymphoma). The medicine is made specially for you from your own white blood cells that have been modified and are known as autologous anti-CD19-transduced CD3+ cells.

Mantle cell lymphoma is a cancer of a part of the immune system (the body's defences). It affects a type of white blood cell called B-lymphocytes. In mantle cell lymphoma, B-lymphocytes grow in an uncontrolled way and build up in the lymph tissue, bone marrow or blood.

How Tecartus works
The white blood cells are taken from your blood and are genetically modified so that they can target the cancer cells in your body. When Tecartus is infused into your blood, the modified white blood cells will kill the cancer cells.

2. What you need to know before you are given Tecartus

You are not to be given Tecartus
- if you are allergic to any of the ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.
- if you can't receive the medicine to reduce the number of white blood cells in your blood (*lymphodepleting chemotherapy*) (see also section 3, How Tecartus is given).

Warnings and precautions
Tecartus is made from your own white blood cells and should only be given to you (*autologous use*).

Tests and checks
Before you are given Tecartus your doctor will:
- Check your lungs, heart, kidney and blood pressure.
- Look for signs of infection or inflammation; and decide whether you need to be treated before you are given Tecartus.
- Check if your cancer is getting worse.
- Look for signs of graft-versus-host disease that can happen after a transplant. This happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhoea and bloody stools.
- Check your blood for uric acid and for how many cancer cells there are in your blood. This will show if you are likely to develop a condition called *tumour lysis syndrome.* You may be given medicines to help prevent the condition.
- Check for hepatitis B, hepatitis C or HIV infection.
- Check if you had a vaccination in the previous 6 weeks or are planning to have one in the next few months.
- Check if you have previously received a treatment that attaches to the protein called CD19.

In some cases, it might not be possible to go ahead with the planned treatment with Tecartus. If Tecartus infusion is delayed for more than 2 weeks after you have received lymphodepleting chemotherapy you may have to receive more chemotherapy (see also section 3, How Tecartus is given).

After you have been given Tecartus
Tell your doctor or nurse immediately or get emergency help right away if you have any of the following:
- Chills, extreme tiredness, weakness, dizziness, headache, cough, shortness of breath, rapid or irregular heartbeat, severe nausea, vomiting, or diarrhoea which may be symptoms of a condition known as *cytokine release syndrome.* Take your temperature twice a day for 3 to 4 weeks after treatment with Tecartus. If your temperature is high, see your doctor immediately.
- Fits, shaking, or difficulty speaking or slurred speech, loss of consciousness or decreased level of consciousness, confusion and disorientation, loss of balance or coordination.
- Fever (e.g. temperature above 38°C), which may be a symptom of an infection.
- Extreme tiredness, weakness and shortness of breath, which may be symptoms of a lack of red blood cells.
- Bleeding or bruising more easily, which may be symptoms of low levels of cells in the blood known as platelets.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse.

Your doctor will regularly check your blood counts as the number of blood cells and other blood components may decrease.

You will be asked to enrol in a registry for at least 15 years in order to better understand the long-term effects of Tecartus.

Do not donate blood, organs, tissues, or cells for transplants.

Children and adolescents
Tecartus should not be used in children and adolescents below 18 years of age.

Other medicines and Tecartus
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

Before you are given Tecartus tell your doctor or nurse if you are taking any medicines that weaken your immune system such as corticosteroids, since these medicines may interfere with the effect of Tecartus.

In particular, you must not be given certain vaccines called live vaccines:
- In the 6 weeks before you are given the short course of lymphodepleting chemotherapy to prepare your body for the Tecartus cells.
- During Tecartus treatment.
- After treatment while the immune system is recovering.

Talk to your doctor if you need to have any vaccinations.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine. This is because the effects of Tecartus in pregnant or breast-feeding women are not known, and it may harm your unborn baby or your breast-fed child.
- If you are pregnant or think you may be pregnant after treatment with Tecartus, talk to your doctor immediately.
- You will be given a pregnancy test before treatment starts. Tecartus should only be given if the results show you are not pregnant.

Discuss pregnancy with your doctor if you have received Tecartus.

Driving and using machines
Tecartus can cause problems such as altered or decreased consciousness, confusion and seizures (fits) in the 8 weeks after it is given.

Do not drive, use machines, or take part in activities that need you to be alert for at least 8 weeks after your Tecartus treatment or until your doctor tells you that you have completely recovered.

Tecartus contains sodium, dimethylsulfoxide (DMSO) and gentamicin
This medicine contains 300 mg sodium (main component of cooking/table salt) in each infusion. This is equivalent to 15% of the recommended maximum daily dietary intake of sodium for an adult. It also contains DMSO and gentamicin which may cause severe hypersensitivity reactions.

3. How Tecartus is given

Tecartus will always be given to you by a healthcare professional.

- Since Tecartus is made from your own white blood cells, your cells will be collected from you to prepare your medicine. Your doctor will take some of your blood using a catheter placed in your vein (a procedure call *leukapheresis*). Some of your white blood cells are separated from your blood and the rest of your blood is returned to your vein. This can take 3 to 6 hours and may need to be repeated.
- Your white blood cells are sent away to a manufacturing center to make your Tecartus. It usually takes about 2 to 3 weeks to make Tecartus but the time may vary.

Medicines given before Tecartus treatment
A few days before you receive Tecartus, you will be given lymphodepleting chemotherapy, which will allow the modified white blood cells in Tecartus to multiply in your body when the medicine is given to you.

During the 30 to 60 minutes before you are given Tecartus you may be given other medicines. This is to help prevent infusion reactions and fever. These other medicines may include:
- Paracetamol.
- An antihistamine such as diphenhydramine.

How you are given Tecartus
Tecartus will always be given to you by a doctor in a qualified treatment centre.

- Tecartus is given in a single dose.
- Your doctor or nurse will give you a single infusion of Tecartus through a catheter placed into your vein (*intravenous infusion*) over about 30 minutes.
- Tecartus is the genetically modified version of your white blood cells. Your healthcare professional handling the treatment will therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases and will follow local guidelines on handling of waste of human-derived material to clean up or dispose of any material that has been in contact with it.

After you are given Tecartus
- You should stay close to the hospital where you were treated for at least 4 weeks after Tecartus treatment. Your doctor will recommend that you return to the hospital daily for at least 10 days or that you stay at the hospital as an in-patient for the first 10 days after Tecartus treatment. This is so your doctor can check if your treatment is working and help you if you have any side effects.

If you miss any appointments, call your doctor or your treatment centre as soon as possible to reschedule your appointment.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Do not try to treat your side effects on your own.

Tecartus can cause side effects that may be serious or life-threatening. **Get urgent medical attention** if you get any of the following side effects after the Tecartus infusion.

Very common: may affect more than 1 in 10 people
- Fever, chills, reduced blood pressure which may cause symptoms such as dizziness, lightheadedness, fluid in the lungs, which may be severe and can be fatal (all symptoms of a condition called *cytokine release syndrome*).
- Loss of consciousness or decreased level of consciousness, confusion or memory loss due to disturbances of brain function, difficulty speaking or slurred speech, involuntary shaking (*tremor*), fits (*seizures*), sudden confusion with agitation, disorientation, hallucination or irritability (*delirium*).
- Fever, chills, which may be signs of an infection.

Other possible side effects
Other side effects are listed below. If these side effects become severe or serious, tell your doctor immediately.

Very common: may affect more than 1 in 10 people
- Abnormally low number of white blood cells, which may increase your risk of infection.
- Low number of cells that help clot the blood *(thrombocytopenia)*, alteration of the blood's ability to form clots: symptoms can include excessive or prolonged bleeding or bruising.
- High blood pressure.
- Decrease in the number of red blood cells (cells that carry oxygen): symptoms can include extreme tiredness with a loss of energy.

– Extreme tiredness.
– Fast or slow heartbeat.
– Decrease of oxygen reaching body tissues: symptoms can include changes to the colour of your skin, confusion, rapid breathing.
– Shortness of breath, cough.
– Nausea, constipation, diarrhoea, abdominal pain, vomiting, difficulty swallowing.
– Muscle pain, joint pain, bone pain, pain in the extremities of the body.
– Lack of energy or strength, muscular weakness, difficulty moving, muscle spasm.
– Headache.
– Kidney problems causing your body to hold onto fluid, build-up of fluids in tissue *(oedema)* which can lead to weight gain and difficulty in breathing, decrease output of urine.
– High levels of uric acid seen in blood tests.
– Low levels of sodium, phosphate, potassium or calcium seen in blood tests.
– Decreased appetite, sore mouth.
– Difficulty sleeping, anxiety.
– Swelling in the limbs, fluid around the lungs *(pleural effusion)*.
– Skin rash.
– Low levels of immunoglobulins seen in blood test, which may lead to infections.
– Increase in liver enzymes seen in blood tests.
– Blood clots: symptoms can include pain in the chest or upper back, difficulty breathing, coughing up blood or cramping pain, swelling in a single leg, warm and darkened skin around the painful area.
– Nerve pain.

Common: may affect up to 1 in 10 people
– Low levels of albumin seen in blood tests.
– Excessive bleeding.
– Irregular heartbeat *(arrhythmia)*.
– Loss of control of body movements.
– Dry mouth, dehydration.
– Breathlessness *(respiratory failure)*.
– Difficulty breathing which makes you unable to speak in full sentence, cough due to fluid in the lungs.
– Increase of the pressure inside your skull.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Tecartus

The following information is intended for doctors only.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the container label and infusion bag after EXP.

Store frozen in vapour phase of liquid nitrogen ≤ − 150 °C until thawed for use.
Do not refreeze.

This medicine contains genetically modified human blood cells. Local guidelines on handling of waste of human-derived material should be followed for unused medicinal product or waste material. As this

medicine will be given by qualified healthcare professionals, they are responsible for the correct disposal of the product. These measures will help protect the environment.

6. Contents of the pack and other information

What Tecartus contains
The active substance is autologous anti-CD19-transduced CD3+ cells. Each patient-specific single infusion bag contains a dispersion of anti-CD19 CAR T cells in approximately 68 mL for a target dose of 2×10^6 anti-CD19 CAR-positive viable T cells/kg.
The other ingredients (excipients) are: Cryostor CS10, sodium chloride, human albumin. See section 2 "Tecartus contains sodium".

What Tecartus looks like and contents of the pack
Tecartus is a clear to opaque, white to red dispersion for infusion, supplied in an infusion bag individually packed in a metal cassette. A single infusion bag contains approximately 68 mL of cell dispersion.

Marketing Authorisation Holder
Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

Manufacturer
Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Gilead Sciences Belgium SRL-BV
Tél/Tel: + 32 (0) 24 01 35 50

България
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Česká republika
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United Kingdom
Gilead Sciences Ltd
Tel: + 44 (0) 8000 113700

This leaflet was last revised in

This medicine has been given ‘conditional approval’.
This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

<--->

The following information is intended for healthcare professionals only:

It is important that you read the entire content of this procedure prior to administering Tecartus.

Precautions to be taken before handling or administering the medicinal product

- Tecartus contains genetically-modified cells. Local guidelines on handling of human-derived material applicable for such products should be followed.
- Tecartus should be transported within the facility in closed, break-proof, leak-proof containers.
- Tecartus is prepared from autologous blood of the patient collected by leukapheresis. Patient leukapheresis material and Tecartus may carry a risk of transmitting infectious viruses to healthcare professionals (HCP) handling the product. Accordingly, HCP should employ appropriate precautions (wearing gloves and glasses) when handling leukapheresis material or Tecartus to avoid potential transmission of infectious diseases.

Preparation for infusion

- Verify that the patient's identity (ID) matches the patient identifiers on the Tecartus metal cassette.
- The Tecartus infusion bag must not be removed from the metal cassette if the information on the patient-specific label does not match the intended patient.
- Once the patient's ID is confirmed, remove the infusion bag from the metal cassette.
- Check that the patient information on the metal cassette label matches that on the bag label.
- Inspect the infusion bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines for handling of waste of human-derived material (or immediately contact Kite).
- Place the infusion bag inside a second bag.
- Thaw Tecartus at approximately 37 °C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Tecartus should not be washed, spun down, and/or re-suspended in new media prior to infusion. Thawing should take approximately 3 to 5 minutes.
- Once thawed, Tecartus is stable at room temperature (20 °C – 25 °C) for up to 3 hours. However, the infusion should begin within 30 minutes of thaw completion.

Do NOT use a leukodepleting filter.

Administration

- The medicine must be administered in a qualified treatment centre by a physician(s) with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Tecartus.
- Ensure that at least 1 dose of tocilizumab per patient and emergency equipment are available prior to infusion and during the recovery period. Hospitals and associated centres should have access to an additional dose of tocilizumab within 8 hours of each previous dose.
- The patient's identity should be matched with the patient identifiers on the infusion bag.
- Tecartus is for autologous use only.
- Tecartus should be administered as an intravenous infusion using latex-free intravenous tubing without a leukocyte depleting filter within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the bag during infusion to prevent cell clumping. All contents of the infusion bag should be infused.
- Sterile sodium chloride 9 mg/mL (0.9%) (0.154 mmol sodium per mL) solution for injection should be used to prime the tubing prior to infusion as well as rinse it afterwards. When the full volume of Tecartus has been infused, the infusion bag should be rinsed with 10 to 30 mL sodium chloride 9 mg/mL (0.9%) solution for injection by back priming to ensure as many cells as possible are infused into the patient.

Disposal of Tecartus

- Any unused medicinal product or waste material that has been in contact with Tecartus (solid and liquid waste) should be handled and disposed of in accordance with local guidelines on handling of waste of human-derived material. Work surfaces and material which have potentially been in contact with Tecartus must be decontaminated with appropriate disinfectant.

Accidental exposure

- Accidental exposure to Tecartus must be avoided. Local guidelines on handling of human-derived material should be followed in case of accidental exposure, which may include washing of the contaminated skin, removal of contaminated clothes.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.

Annex 4. Kite Signature Page

KITE PHARMA INC.

LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF TECARTUS FOR TREATMENT OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA (MCL)

ORIGINAL, 18 FEBRUARY 2021
VERSION 1.1, 13 JULY 2021
VERSION 1.2, 10 NOVEMBER 2021

This protocol has been approved by Kite Pharma Inc. The following signatures document this approval.

Dr. Heribert Ramroth

Study Director (Printed)
Author

DocuSigned by:
2DA6CC5FF4C340B...

Signature

November 18, 2021 | 6:56:40 AM PST

Date

Dr. Anne-Ruth van Troostenburg de Bruyn

Kite Gilead EU QPPV (Printed)

DocuSigned by:
Anna van Troostenburg
ED6C40238C864B2...

Signature

November 18, 2021 | 7:06:31 AM PST

Date

Annex 5. Cellular and Gene Therapy Form

EBMT Cellular and Gene Therapy Form provided for entries in the EBMT Registry at the time point of this protocol version. During the course of the study updated versions of this form will be provided as appendices of annual reports (see Section 10.1.2).

Advanced Cellular Therapies Form

Pre-treatment Registration

EBMT Unique Identification Code (UIC) ..... **(Please complete if the patient had a previous treatment and is already registered in the database)** ID.IDAA
(if applicable)

CENTRE IDENTIFICATION

EBMT Centre Identification Code (CIC): .... CENTRNR

Main indication for the therapy: INDICAT
- ☐ Primary disease including Infections with or w/o a previous HSCT
- ☐ SCT related complication: GvHD, Graft failure / Prevention, Treatment
- ☐ Both: Primary disease AND Complications

Unit: ..... UNIT

Type of unit or team for this Cellular therapy: TEAMTYPE
(Optional: It is a coded replication of Unit, the item above, and it is for centres which have more than one department or unit reporting to the EBMT.)

- ☐ Haematology
- ☐ Adults
- ☐ Allograft
- ☐ BMT unit
- ☐ Paediatric oncology
- ☐ Oncology
- ☐ Paediatrics
- ☐ Autograft
- ☐ Paediatric haematology
- ☐ Dept. Medicine

Contact person..... MEDNAME

PATIENT DATA

Date of this Report: ..... - ..... - .....
DAT1STRE *yyyy mm dd*

Hospital Unique Patient Number or Code (UPN): ..... UPN
Compulsory, registrations will not be accepted without this item. *All treatments performed in the same patient must be registered with the same patient identification number or code as this belongs to the patient and not to the treatment.*

Other type of patient identification codes ..... VDOSSIER
(Optional: This item is to be used by the centre to register a patient code for internal use as necessary)

Initials: ....._..... (first name(s) _family name(s)) GIVNAME FAMNAME

Date of Birth: ..... - ..... - ..... DATPATBD
yyyy mm dd

Sex: ☐ Male ☐ Female PATSEX
(at birth)

ABO Group .... ABOPAT

Rh factor: ☐ Absent ☐ Present ☐ Not evaluated RHESPAT

Important:
If the patient had a previous Cellular Therapy or a stem cell transplant please make sure that this previous treatment is registered and that the latest follow up was recorded using appriopriate follow up form before proceeding. This is so we can capture relapse data and other events between the transplant/advanced cellular therapy.

INDICATION FOR ADVANCED CELLULAR THERAPY TREATMENT

SELECT ALL THAT APPLY

☐ Treatment of a Primary disease

Date of initial diagnosis: ..... - ..... - ..... IDAABB
yyyy mm dd

DISMCLFD

INDICATE THE PRIMARY DISEASE OF THE PATIENT WHO RECEIVED THIS THERAPY

☐ Primary Acute Leukaemia VACLEUK
- ☐ Acute myelogenous leukaemia (Page 8) AML
- ☐ Precursor lymphoid neoplasms (Page 12) ALLL
- ☐ Other Primary Acute Leukaemia (Page 15)

☐ Chronic Leukaemia VCHRLEUK
- ☐ Chronic Myeloid Leukaemia (CML) (Page 16)
- ☐ Chronic Lymphocytic Leukaemia (CLL) (Page 17)
- ☐ Prolymphocytic Leukaemia (PLL) (Page 18) VCPLSUBC

☐ Lymphoma WHOLYCLS (Page 19)
- ☐ Non Hodgkin
- ☐ Hodgkin Lymphoma HODGKIN (Page 22)

☐ Myelodysplastic syndrome and/or myeloproliferative neoplasm VMDSMPS
- ☐ MDS MDSSTAG (Page 24)
- ☐ MDS/MPN MDSAMPS (Page 27)
- ☐ Myeloproliferative neoplasm VMPS (Page 29)

☐ Myeloma /Plasma cell disorder VPLCEDS1 (Page 31)

☐ Aplastic Anaemia and Other Bone Marrow Failure Syndromes BMFTYPE BMFSACQ (Page 33)

☐ Haemoglobinopathy VHEMOGLO (Page 34)

☐ Solid Tumour VSOLTUMO (Page 35)

☐ Inherited disorders INHDIS (Page 37)
- ☐ Primary immune deficiencies IMMDEF
- ☐ Metabolic disorders VINBERR2
- ☐ Other (Page 38)

☐ Histiocytic disorders HISTIOCY (Page 39)

☐ Autoimmune disease VAUTOIM1
- ☐ Connective VAUTOIM2 (Page 40)
- ☐ Vasculitis VAUTOIM3 (Page 40)
- ☐ Arthritis VAUTOIM4 (Page 41)
- ☐ Neurological (MS, etc) VAUTOIM5 (Page 41)
- ☐ Haematological VAUTOIM6 (Page 41)
- ☐ Bowel disorder VAUTOIM7 (Page 42)
- ☐ Other (Diabetes, etc.) VAUTOIM8 (Page 42)

☐ Infections INFTRTAIM (Page 44)

Other primary disease (Page 43)
(check disease classification sheets for options)
☐ Specify ..... VDIAGTX

Complete and attach the relevant DISEASE CLASSIFICATION SHEET as per the page numbers indicated above, including the date of Advanced Cellular therapy and disease status at treatment, then continue from here.

☐ **Treatment or prevention of complications derived from a previous treatment including HSCT or expected from a subsequent treatment**

➡ **Please make sure that MedAB form was registered for the Transplant indicated above and that an Annual follow up form is recorded before proceeding. This is so we can capture relapse data and other events between the transplant/advanced cellular therapy.**

☐ **Other indication, specify**:_____ VDIAGTX

Please, contact the Registry helpdesk before proceeding: ***registryhelpdesk@ebmt.org***

Date of the cell collection (apheresis) ..... - ..... - ..... IDAABC
If more than one collection use the date of the first collecition
yyyy mm dd

BASIC INFORMATION ON THE ADVANCED CELLULAR THERAPY

Clinical setting: CTCLNSETTN
(Select only one)

- ☐ As per marketing approval / Standard of care
- ☐ Institutional guidelines
- ☐ Hospital exemption
- ☐ Compassionate use / Accelerated access

PASSSTUDY
Is patient enrolled in a IV / PASS study? ☐ No ☐ Yes

☐ Investigational DP / Clinical trial (CT)

CTCLNPHASE Phase ☐ 1 ☐ 1/2 ☐ 2 ☐ 2/3 ☐ 3

CTCLNBLIND Blind trial ☐ No ☐ Yes

CTCLNRAND Randomised trial ☐ No ☐ Yes

Eudract number…….. USA CT number…… UMIN CT number……
CTEUDRANUM CTUSANUMB CTJAPANUMB *(Japan)*

☐ Tick here if you want this registration hidden until ..... - ..... - .....
(indicate by which date the registration can be made available for research) HIDEREG DATHIDEREG
yyyy mm dd

Cell origin CETHORIG

- ☐ Autologous -> Go to page 6 *CELLULAR THERAPY INFUSION UNIT*
- ☐ Allogeneic

This product is manufactured from: COMMANFPRD

- ☐ A known donor never used before to treat this patient -> Complete DONOR section on page 5
  (eg. from a Donor registry or related)
- ☐ A donor that is already registered as part of a previous treatment
  -> Skip DONOR section on page 5
- ☐ An unknown donor with not available data -> Skip DONOR section on page 5
  (eg. from a commercial product)

Donor

Donor information

Global registration identifier for donors…… …….. GRID

HLA match type DONRL

- ☐ HLA-identical sibling *(may include non-monozygotic twin)*
- ☐ Syngeneic *(monozygotic twin)*
- ☐ HLA-matched other relative
- ☐ HLA-mismatched relative: Degree of mismatch ALLMISRL ☐ 1 HLA locus mismatch ☐ ≥ 2 HLA loci mismatch

Donor ID given by the treating centre DONORID2

☐ Unrelated donor

ION code of the Donor Registry or Cord Blood Bank (*up to 4 characters*) .... IONDR

Name of donor registry or Cord Blood Bank .... DONREGID CBBANKID

Donor ID given by the Donor Registry or the Cord Blood Bank ..... ….DONORID DONORID1

Eurocord code for the Cord Blood Bank *(complete only if applicable)* …… EUROCID

Date of birth : .... - .... - .... DATDONBD *yyyy mm dd*

OR

Age at time of donation……. *years* ……. *months* *(if date of birth not provided)* AGEDONYR AGEDONMTH

Donor Sex ***(at birth)*** ☐ Male ☐ Female DONSEX

CELLULAR THERAPY INFUSION UNIT(S)

Was it planned to administer more than one cell infusion unit during the treatment

☐ No MNYINFUSED

☐ Yes: Indicate number of cell infusion units for this CT treatment ..... NUMCINFUNIT

Cellular Therapy Infusion Unit – Description and collection

If more than one cell infusion unit, replicate this section for each one of them

IDENTIFICATION

Name of the manufacturer ..... ☐ N/A NAMCTIMNFCD NAMCTIMNFSP
Enter Hospital name if it isn't a commercial product

Name of the product *(if applicable)* ..... NAMCTIPKGCD NAMCTIPKGSP

TISSUE SOURCE *(check all that apply)*

☐ Bone Marrow CIUBMRRW ☐ Peripheral Blood CIUPFRBLD ☐ Umbilical cord Blood CIUUMBCBLD

☐ Tumour CIUTUMRTIS ☐ Other, specify ..... CIUOTHSRC CIUOTHRSPC

CELL TYPES

☐ CD3+ lymphocytes CIUCELCD3 ☐ CD4+ lymphocytes CIUCELCD4 ☐ CD8+ lymphocytes CIUCELCD8

☐ Gamma-Delta T-cells CIUGADETCELL ☐ Regulatory T-cells REGTCELLS ☐ Mesenchymal CIUCELMESN

☐ Dendritic cells CIUCELDNDR ☐ CD34+ CIUCELCD34 ☐ NK cells CIUCELNK

☐ Mononuclear cells (DLI) CIUCELMON ☐ Other, specify ..... CIUCELOTHR CIUCELOTSPC

COLLECTION PROCEDURE

Date of the collection ..... - ..... - ..... CIUCOLLDAT
If more than one collection use the date of the first collecition
yyyy mm dd

Number of collections ..... CIUNUMCOLL

Survival Status

VPATSTAT

☐ Alive ☐ Dead

If dead: Main Cause of Death *(check only one main cause)*: VCAUSDTH

☐ Relapse or Progression/Persistent disease
☐ Secondary malignancy
☐ Cellular Therapy related (indicate all toxicity related causes of death below)
☐ HSCT Related Cause (only if patient previously had a transplant / indicate all toxicity related causes of death below)
☐ Unknown
☐ Other: ..... DEACSBMU

Indicate toxicity related causes of death *(check as many as appropriate)*:
☐ GVHD VCSDTGVH
☐ Cytokine release syndrome VCSDTCRS
☐ Interstitial pneumonitis VCSDTINP
☐ Pulmonary toxicity VCSDTPTX
☐ Infection: VCSDTINF
  ☐ bacterial VCSDTBAC
  ☐ viral VCSDTVIR
  ☐ fungal VCSDTFUN
  ☐ parasitic VCSDTPAR
☐ Rejection/Poor graft function VCSDTREJ
☐ History of severe Veno occlusive disorder (VOD) VCSDTVOD
☐ Haemorrhage VCSDTHMR
☐ Cardiac toxicity VCSDTCTX
☐ Central nervous system (CNS) toxicity VCSDTCNS
☐ Gastrointestinal (GI) toxicity VCSDTGIT
☐ Skin toxicity VCSDTSKI
☐ Renal failure VCSDTREN
☐ Multiple organ failure VCSDTMOF

☐ Other:..... DEACSBMR

END OF PRE-TREATMENT REGISTRATION

ACUTE LEUKAEMIAS VACLEUK

Acute Myeloid Leukaemia (AML) (1 of 4)

(main disease code 1)

Disease

Classification: AML

AML with recurrent genetic abnormalities

- ☐ AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
- ☐ AML with inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); CBFB-MYH11
- ☐ Acute promyelocytic leukaemia with t(15;17)(q22;q12); PML/RARA
- ☐ AML with t(9;11) (p22;q23); MLLT3-MLL
- ☐ AML with t(6;9) (p23;q24); DEK-NUP214
- ☐ AML with inv(3) (q21;q26.2) or t(3;3) (q21;q26.2); RPN1-EVI1
- ☐ AML (megakaryoblastic) with t(1;22) (p13;q13); RBM15-MKL1
- ☐ AML with myelodysplasia related changes (old "Acute leukaemia transformed from MDS or MDS/MPN"):

  Was there a previous diagnosis of MDS or MDS/MPN? PREVMDS

  - ☐ No → *Continue to PREDISPOSING CONDITION below*
  - ☐ Yes → *Fill in the* MYELODYPLASTIC SYNDROME (MDS) (page 24) or MDS/MPN (page 27) *until status at Cellular Therapy, then continue with PREDISPOSING CONDITION below*

- ☐ AML with 11q23 (MLL) abnormalities
- ☐ AML with BCR-ABL1
- ☐ AML with mutated NPM1
- ☐ AML with biallelic mutation of CEBPA
- ☐ AML with mutated RUNX1

AML not otherwise categorised (NOS)

- ☐ AML with minimal differentiation (FAB M0)
- ☐ AML without maturation (FAB M1)
- ☐ AML with maturation (FAB M2)
- ☐ Acute myelomonocytic leukaemia (FAB M4)
- ☐ Acute monoblastic and monocytic leukaemia (FAB M5)
- ☐ Acute erythroid leukaemia (FAB M6)
- ☐ Acute megakaryoblastic leukaemia (FAB M7)
- ☐ Acute basophilic leukaemia
- ☐ Acute panmyelosis with myelofibrosis

- ☐ Myeloid sarcoma
- ☐ Myeloid proliferations related to Down syndrome
- ☐ Blastic plasmacytoid dendritic cell neoplasm (BPDCN)
- ☐ Therapy related myeloid neoplasia *(old "Secondary Acute Leukaemia")*

  Related to prior treatment but NOT after a previous diagnosis of MDS or MPN

PREDISPOSING CONDITION?

Did the recipient have a predisposing condition prior to the diagnosis of leukaemia? VPRECOND VPREDISP

☐ No ☐ Yes:
- ☐ Aplastic anaemia
- ☐ Bloom syndrome
- ☐ Fanconi anaemia
- ☐ Unknown

Donor cell leukaemia?

IF THE PATIENT HAS RECEIVED AN ALLOGRAFT TRANSPLANT PRIOR TO THE DIAGNOSIS OF ACUTE LEUKAEMIA, ANSWER THE FOLLOWING QUESTION

Is this a donor cell leukaemia ☐ No ☐ Yes ☐ Not evaluated ☐ Unknown RPDRGRAD

ACUTE MYELOID LEUKAEMIA (AML) (2 of 4)

Chromosome analysis at diagnosis (All methods including FISH)
Chromosome / genetic analysis done? ☐ No *(skip this section)* ☐ Yes *(continue with this section)*

☐ Normal VCHROMOS

☐ Abnormal:

Complex karyotype: ☐ No ☐ Yes ☐ Unknown MORE3AB
(3 or more abnormalities)

Monosomal karyotype: ☐ No ☐ Yes ☐ Unknown MONOSKAR
(≥ 2 autosomal monosomies or 1 autosomal monosomy + at least 1 structural abnormality)

☐ Unknown

You can transcribe the complete karyotype: .....
CHRMABND **OR**

Indicate below those abnormalities that have been **evaluated** and whether they were **Absent** or **Present** IDAABECC

t(15;17) CHROPRES	☐ Absent	☐ Present	☐ Not evaluated
t(8;21)	☐ Absent	☐ Present	☐ Not evaluated
inv(16)/ t(16;16)	☐ Absent	☐ Present	☐ Not evaluated
11q23 abnormality type	☐ Absent	☐ Present	☐ Not evaluated
Fill only if 11q23 abnormality is Present:			
t(9;11)	☐ Absent	☐ Present	☐ Not evaluated
t(11;19)	☐ Absent	☐ Present	☐ Not evaluated
t(10;11)	☐ Absent	☐ Present	☐ Not evaluated
t(6;11)	☐ Absent	☐ Present	☐ Not evaluated
Other abn(11q23), specify: _ _ _ _ _ CHRMABND	☐ Absent	☐ Present	☐ Not evaluated
3q26 (EVI1) abnormality type	☐ Absent	☐ Present	☐ Not evaluated
Fill only if 3q26 (EVI1) abnormality is Present:			
inv(3) / t(3;3)	☐ Absent	☐ Present	☐ Not evaluated
t(2;3)(p21;q26)	☐ Absent	☐ Present	☐ Not evaluated
Other (3q26)/EVI1 rearrangement, specify: _ _ _ _ _ CHRMABND	☐ Absent	☐ Present	☐ Not evaluated
t(6;9)	☐ Absent	☐ Present	☐ Not evaluated
abn 5 type	☐ Absent	☐ Present	☐ Not evaluated
Fill only if above abn 5 is Present:			
del (5q)	☐ Absent	☐ Present	☐ Not evaluated
monosomy 5	☐ Absent	☐ Present	☐ Not evaluated
Add(5q)	☐ Absent	☐ Present	☐ Not evaluated
Other abn(5q); please specify: _ _ _ _ _ CHRMABND	☐ Absent	☐ Present	☐ Not evaluated
abn 7 type	☐ Absent	☐ Present	☐ Not evaluated
Fill only if abn 7 is Present:			
del(7q)	☐ Absent	☐ Present	☐ Not evaluated
monosomy 7	☐ Absent	☐ Present	☐ Not evaluated
add(7q)	☐ Absent	☐ Present	☐ Not evaluated
Other abn(7q); please specify: _ _ _ _ _ CHRMABND	☐ Absent	☐ Present	☐ Not evaluated
-17	☐ Absent	☐ Present	☐ Not evaluated
Abn(17p)	☐ Absent	☐ Present	☐ Not evaluated
t(1;22)	☐ Absent	☐ Present	☐ Not evaluated
trisomy 8	☐ Absent	☐ Present	☐ Not evaluated
Other, specify..... CHRMABND	☐ Absent	☐ Present	

ACUTE MYELOID LEUKAEMIA (AML) (3 of 4)

Molecular Markers at Diagnosis

Molecula analysis done? ☐ No *(skip this section)* ☐ Yes *(continue with this section)*

Molecular marker analysis at diagnosis MOLEBIO

☐ Absent ☐ Present ☐ Unknown

Indicate below those **markers** that have been **evaluated** and whether they were **Absent** or **Present**

IDAABECL MOLPRES

AML1-ETO (RUNX1/RUNXT1) *Molecular product of t(8;21)*	☐ Absent	☐ Present	☐ Not evaluated
CBFB-MYH11 *Molecular product of inv(16)(p13.1;q22) or (16;16)(p13.1;q22)*	☐ Absent	☐ Present	☐ Not evaluated
PML-RARα *Molecular product of t(15;17)*	☐ Absent	☐ Present	☐ Not evaluated

MLL-rearrangement/mutation: *Fill only if* 11q23 abnormality *is Present:*	☐ Absent	☐ Present	☐ Not evaluated
MLLT3(AF9)-MLL *molecular product of t(9;11)(p22;q23)*	☐ Absent	☐ Present	☐ Not evaluated
MLL-PTD (partial tandem duplication)	☐ Absent	☐ Present	☐ Not evaluated
MLLT4(AF6)-MLL *molecular product of t(6;11)(q27;q23)*	☐ Absent	☐ Present	☐ Not evaluated
ELL-MLL: *molecular product of t(11;19)(q23;p13.1)*	☐ Absent	☐ Present	☐ Not evaluated
MLLT1(ENL)-MLL: *molecular product of t(11;19)(q23;p13.3)*	☐ Absent	☐ Present	☐ Not evaluated
MLLT10(AF10)-MLL: *molecular product of t(10;11)(p12;q23)*	☐ Absent	☐ Present	☐ Not evaluated
Other MLL-rearrangement, specify: …… MOLOTHER	☐ Absent	☐ Present	☐ Not evaluated

DEK-NUP214(CAN) *molecular product of translocation t(6;9)(p23;q34)*	☐ Absent	☐ Present	☐ Not evaluated
RPN1-EVI1 *molecular product of inv(3)(q21q26.2) or t(3;3)(q21q26.2)*	☐ Absent	☐ Present	☐ Not evaluated
RBM15-MKL1 *molecular product of translocation t(1;22)(p13;q13)*	☐ Absent	☐ Present	☐ Not evaluated
NPM1 mutation	☐ Absent	☐ Present	☐ Not evaluated
CEBPA mutation	☐ Absent	☐ Present	☐ Not evaluated
FLT3-ITD *(internal tandem duplication)*	☐ Absent	☐ Present	☐ Not evaluated
DNMT3A	☐ Absent	☐ Present	☐ Not evaluated
ASXL1	☐ Absent	☐ Present	☐ Not evaluated
TP53	☐ Absent	☐ Present	☐ Not evaluated
RUNX1	☐ Absent	☐ Present	☐ Not evaluated
c-KIT	☐ Absent	☐ Present	☐ Not evaluated
Other, specify…… MOLOTHER	☐ Absent	☐ Present	☐ Not evaluated

ACUTE LEUKAEMIAS
Primary Acute Myeloid Leukaemia (AML) (4 of 4)

Involvement at Diagnosis

Was Involvement assessed ☐ No *(skip this section)* ☐ Yes *(continue with this section)*

Involvement at diagnosis IDAABECK

Bone marrow	☐ No	☐ Yes	☐ Not evaluated	ORGANOT
CNS	☐ No	☐ Yes	☐ Not evaluated	
Testes/ovary	☐ No	☐ Yes	☐ Not evaluated	
Other	☐ No	☐ Yes, specify		ORGANOTS

Status at Cellular Therapy

STATUS VDISESTA	NUMBER	TYPE OF REMISSION	
☐ Primary induction failure	VNUMSTM		
☐ Complete haematological remission (CR)	☐ 1st ☐ 2nd ☐ 3rd or higher	CYTOGENETIC REMISSION ☐ No VCYTOGRE ☐ Yes ☐ Not evaluated ☐ Not applicable* ☐ Unknown	MOLECULAR REMISSION ☐ No VMOLECRE ☐ Yes ☐ Not evaluated ☐ Not applicable* ☐ Unknown
☐ Relapse	☐ 1st ☐ 2nd ☐ 3rd or higher		

* *No abnormalities detected prior to this time point*

Date of last relapse before this Cellular Therapy: ..... DATLRLPS
(If applicable) *yyyy - mm - dd*

ACUTE LEUKAEMIAS

Precursor lymphoid neoplasms *(previously ALL)* (main disease code 1)

Disease

Classification: ALLL

- ☐ B lymphoblastic leukaemia/lymphoma NOS *(old Precursor B-cell ALL)*
  - ☐ with t(9;22)(q34;q11.2); *BCR-ABL1*
  - ☐ with t(v;11q23); *MLL* rearranged
  - ☐ with t(12;21)(p13;q22); *TEL-AML1 (ETV-RUNX1)*
  - ☐ with hyperdiploidy
  - ☐ with hypodiploidy
  - ☐ with t(5;14)(q31;q32); *IL3-IGH*
  - ☐ with t(1;19)(q23;p13.3); *E2A-PBX1*
  - ☐ Not otherwise specified (NOS)
  - ☐ Other._____
- ☐ T lymphoblastic leukaemia/lymphoma *(old Precursor T-cell ALL)*

Secondary Origin?

Secondary origin

Related to prior exposure to therapeutic drugs or radiation ☐ No VSECORIG ☐ Yes ☐ Unknown

IF THE PATIENT HAS RECEIVED AN ALLOGRAFT PRIOR TO THE DIAGNOSIS OF ACUTE LEUKAEMIA, ANSWER THE FOLLOWING QUESTION

Is this a donor cell leukaemia ☐ No ☐ Yes ☐ Not evaluated ☐ Unknown

RPDRGRAD

PRECURSOR LYMPHOID NEOPLASMS (previously ALL)

Chromosome Analysis at Diagnosis

Chromosome / genetic analysis done? ☐ No *(skip this section)* ☐ Yes *(continue with this section)*

Chromosome analysis at diagnosis (All methods including FISH) VCHROMOS

☐ Normal ☐ Abnormal ☐ Unknown

MORE3AB If abnormal:

Complex karyotype: ☐ No ☐ Yes ☐ Unknown

(3 or more abnormalities)

CHRMABND

You can transcribe the complete karyotype: .....

OR

Indicate below which abnormalities have been **evaluated** and whether they were **Absent** or **Present** IDAABECC CHROPRES

t(9;22)	☐ Absent	☐ Present	☐ Not evaluated
11q23 abnormalities *Fill only if* 11q23 abnormalities *is Present:*	☐ Absent	☐ Present	☐ Not evaluated
t(4;11)	☐ Absent	☐ Present	☐ Not evaluated
Other abn(11q23); please specify: _ _ _ _ _ CHRMABND	☐ Absent	☐ Present	☐ Not evaluated
t(12;21)	☐ Absent	☐ Present	☐ Not evaluated
hyperdiploidy (>46 chromosomes) *Fill only if* hyperdiploidy *is Present:*	☐ Absent	☐ Present	☐ Not evaluated
50 – 66 chromosomes	☐ Absent	☐ Present	☐ Not evaluated
Trisomy: Specify extra chromosome _ _ _ _ _ CHRMABND	☐ Absent	☐ Present	☐ Not evaluated
Other hyperdiploid karyotype ..... number of chromosomes ..... NRCHROMS	☐ Absent	☐ Present	☐ Not evaluated
Hypodiploidy (<46 chromosomes): *Specify the number of missing chromosomes:*	☐ Absent	☐ Present	☐ Not evaluated
Low hypodiploid, 32-39 chromosomes	☐ Absent	☐ Present	☐ Not evaluated
Near haploid, 24-31 chromosomes	☐ Absent	☐ Present	☐ Not evaluated
Monosomy. Specify: ..... CHRMABND	☐ Absent	☐ Present	☐ Not evaluated
Other. number of chromosomes ..... NRCHROMS	☐ Absent	☐ Present	☐ Not evaluated
t(5;14)(q31;q32)	☐ Absent	☐ Present	☐ Not evaluated
t(1;19)	☐ Absent	☐ Present	☐ Not evaluated
trisomy 8	☐ Absent	☐ Present	☐ Not evaluated
Other, specify..... CHRMABND	☐ Absent	☐ Present	☐ Not evaluated

PRECURSOR LYMPHOID NEOPLASMS (previously ALL)

Molecular Markers at Diagnosis

Molecula analysis done? ☐ No *(skip to WHITE BLOOD CELL COUNT)* ☐ Yes *(continue with this section)*

Marker analysis MOLEBIO
☐ Absent ☐ Present ☐ Unknown

Indicate below those **markers** that have been **evaluated** and whether they were **Absent** or **Present** IDAABECL MOLPRES

BCR-ABL *molecular product of t(9;22)(q34;q11.2)*	☐ Absent	☐ Present	☐ Not evaluated
MLL-rearrangement/mutation	☐ Absent	☐ Present	☐ Not evaluated
Fill only if MLL-rearrangement/mutation *is Present:*			
AFF1(AF4)-MLL *molecular product of t(4;11)(q21;q23)*	☐ Absent	☐ Present	☐ Not evaluated
MLLT1(ENL)-MLL *molecular product of t(11;19)(q23;p13.3)*	☐ Absent	☐ Present	☐ Not evaluated
MLLT3(AF9)-MLL *molecular product of t(9;11)(p22;q23)*	☐ Absent	☐ Present	☐ Not evaluated
MOLOTHER Other MLL-rearrangement, specify: ……	☐ Absent	☐ Present	☐ Not evaluated
TEL(ETV6)-AML1(RUNX1) *molecular product of t(12;21)(p13;q22)*	☐ Absent	☐ Present	☐ Not evaluated
IL3-IGH *molecular product of translocation t(5;14)(q31;q32)*	☐ Absent	☐ Present	☐ Not evaluated
TCF3-PBX1 *Molecular product of translocation (1;19)(q23 ;p13.3)*	☐ Absent	☐ Present	☐ Not evaluated
IKZF1 (IKAROS)	☐ Absent	☐ Present	☐ Not evaluated
NOTCH1 & FBXW7	☐ Absent	☐ Present	☐ Not evaluated
Other, specify…… MOLOTHER	☐ Absent	☐ Present	☐ Not evaluated

White blood cell count at diagnosis (10^9/l): .... - .... ☐ Not available / unknown WBCD

Status at Cellular Therapy

STATUS VDISESTA	NUMBER VNUMSTM	TYPE OF REMISSION	
		CYTOGENETIC REMISSION	MOLECULAR REMISSION
☐ Primary induction failure			
☐ Complete haematological remission (CR) ☐ CRi (CR with incomplete haematologic recovery)	☐ 1st ☐ 2nd ☐ 3rd or higher	☐ No VCYTOGRE ☐ Yes ☐ Not evaluated ☐ Not applicable* ☐ Unknown	☐ No VMOLECRE ☐ Yes ☐ Not evaluated ☐ Not applicable* ☐ Unknown
☐ Relapse	☐ 1st ☐ 2nd ☐ 3rd or higher		

* *No abnormalities detected prior to this time point*

ACUTE LEUKAEMIAS

Other Acute Leukaemias (main disease code 1)

Disease

Classification: VACLEUK

Acute Leukaemias of ambiguous lineage

- ☐ Acute undifferentiated leukaemia
- ☐ Mixed phenotype NOS
  - ☐ Mixed phenotype B/myeloid, NOS
  - ☐ Mixed phenotype T/myeloid, NOS
- ☐ Natural killer (NK)- cell lymphoblastic leukaemia/lymphoma
- ☐ Other, specify.....

Secondary Origin?

Secondary origin

Related to prior exposure to therapeutic drugs or radiation ☐ No VSECORIG ☐ Yes ☐ Unknown

IF THE PATIENT HAS RECEIVED AN ALLOGRAFT PRIOR TO THE DIAGNOSIS OF ACUTE LEUKAEMIA, ANSWER THE FOLLOWING QUESTION

Is this a donor cell leukaemia ☐ No ☐ Yes ☐ Not evaluated ☐ Unknown

RPDRGRAD

Status at Cellular Therapy

STATUS VDISESTA	NUMBER VNUMSTM	TYPE OF REMISSION	
☐ Primary induction failure			
☐ Complete haematological remission (CR)	☐ 1st ☐ 2nd ☐ 3rd or higher	CYTOGENETIC REMISSION ☐ No VCYTOGRE ☐ Yes ☐ Not evaluated ☐ Not applicable* ☐ Unknown	MOLECULAR REMISSION ☐ No VMOLECRE ☐ Yes ☐ Not evaluated ☐ Not applicable* ☐ Unknown
☐ Relapse	☐ 1st ☐ 2nd ☐ 3rd or higher		

* *No abnormalities detected prior to this time point*

CHRONIC LEUKAEMIAS
Chronic Myelogenous Leukaemias (CML) (main disease code 2)

Disease

Classification: *(CMML is not a CML but MDS/MPN)* IDAABECC CHROPRES
At least one investigation must be positive

Translocation (9;22)	☐ Absent	☐ Present	☐ Not evaluated
bcr-abl	☐ Absent	☐ Present	☐ Not evaluated

Status at Cellular Therapy

PHASE VDISESTA	NUMBER VNUMSTM	TYPE OF REMISSION		
		HAEMATOLOGICAL	CYTOGENETIC	MOLECULAR
☐ Chronic phase (CP)	☐ 1st ☐ 2nd ☐ 3rd or higher	☐ Yes VREMTRAN ☐ No ☐ Not evaluated ☐ Unknown	☐ Yes VCYTOGRE ☐ No ☐ Not evaluated ☐ Not applicable* ☐ Unknown	☐ Yes VMOLECRE ☐ No ☐ Not evaluated ☐ Not applicable* ☐ Unknown
☐ Accelerated phase	☐ 1st ☐ 2nd ☐ 3rd or higher			
☐ Blast crisis	☐ 1st ☐ 2nd ☐ 3rd or higher			

* *No abnormality detected prior to this time point*

CHRONIC LEUKAEMIAS
Chronic Lymphocytic leukaemias (CLL) (main disease code 2)

Disease

Classification: VCLLSUBC

☐ Chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma

☐ Richter's syndrome VCLLSUBC

Transformed from a previously known CLL VSECORIG

☐ Yes: Date of original CLL diagnosis .... - .... - .... IDAABB
yyyy mm dd

☐ No: Primary Richter *(without previous known diagnosis of CLL)*

CYTOGENETICS AT DIAGNOSIS (ALL METHODS INCLUDING FISH)

Chromosome / genetic analysis done? ☐ No *(skip to MOLECULAR MARKERS)* ☐ Yes *(continue with this section)*

☐ Done: Normal ☐ Done: Abnormal ☐ Unknown VCHROMOS

IDAABECC CHROPRES

CLL and Richter			
Trisomy 12	☐ Absent	☐ Present	☐ Not evaluated
Del 13q14	☐ Absent	☐ Present	☐ Not evaluated
Del 11q22-23	☐ Absent	☐ Present	☐ Not evaluated
del(17p)	☐ Absent	☐ Present	☐ Not evaluated
Other, specify .....CHRMABND	☐ Absent	☐ Present	☐ Not evaluated

MOLECULAR MARKERS AT DIAGNOSIS MOLEBIO MOLPRES

Molecula analysis done? ☐ No *(skip next question)* ☐ Yes *(continue with the next question)*

TP53 mutations ☐ Absent ☐ Present ☐ Not evaluated ☐ unknown

Status at Cellular Therapy

STATUS VDISESTA	MINIMAL RESIDUAL DISEASE (MRD) *(by FACS or PCR)* VMFACPCR
☐ Complete remission (CR) ☐ Partial response (PR)	☐ Negative ☐ Positive ☐ Not evaluated
☐ Stable disease (SD) ☐ Relapse *(untreated)* ☐ Progression (PD) ☐ Never treated	

CHRONIC LEUKAEMIAS
Prolymphocytic and Other leukaemias (PLL & Other) (main disease code 2)

Disease

☐ Prolymphocytic Leukaemia (PLL) VCPLSUBC
- ☐ PLL, B-cell
- ☐ PLL, T-cell

☐ Hairy Cell Leukaemia VCLLSUBC

☐ Other leukaemia, specify:_____ VDIAGTX

T-CELL PLL ONLY - IMMUNOPHENOTYPING of T-cells at diagnosis

NOTE: TdT *(Terminal deoxynucleotidyl transferase)* must be negative

CD4+	☐ No	☐ Yes	☐ Not evaluated	VPIMMCD4
CD8+	☐ No	☐ Yes	☐ Not evaluated	VPIMMCD8

PLL ONLY - CYTOGENETICS AT DIAGNOSIS (ALL METHODS INCLUDING FISH) VCHROMOS

Chromosome / genetic analysis done? ☐ No *(skip to LYMPHOCYTE COUNT)* ☐ Yes *(continue with the next question)*

☐ Done: Normal ☐ Done: Abnormal ☐ Unknown VCHROMOS

IDAABECC CHROPRES

inv(14)/ t(14:14) (q11q32)	☐ Absent	☐ Present	☐ Not evaluated
del(14)(q12)	☐ Absent	☐ Present	☐ Not evaluated
t(11:14)(q23;q11)	☐ Absent	☐ Present	☐ Not evaluated
t(7:14)(q35:q32.1)	☐ Absent	☐ Present	☐ Not evaluated
t(X:14)(q35:q11)	☐ Absent	☐ Present	☐ Not evaluated
idic(8) (p11)	☐ Absent	☐ Present	☐ Not evaluated
Other, specify ……CHRMABND	☐ Absent	☐ Present	☐ Not evaluated

Lymphocyte count …… 10^9 cells/L LYMPHOC

Status at Cellular Therapy

STATUS VDISESTA
- ☐ Complete remission (CR)
- ☐ Partial remission (PR)
- ☐ Stable disease (SD)
- ☐ Untreated Relapse
- ☐ Progression (PD)
- ☐ Never treated

LYMPHOMAS
B-Cell Non Hodgkin Lymphomas (NHL) (main disease code 3)

Disease

Mature B-cell Neoplasms WHOLYCLS	**Complete only for corresponding classifications from the left side**
☐ Splenic marginal zone lymphoma	
☐ Extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT)	
☐ Nodal marginal zone lymphoma	
☐ Lymphoplasmacytic lymphoma (LPL)	
☐ Waldenstrom macroglobulinaemia (LPL with monoclonal IgM)	**International Prognostic Scoring System for Waldenström's Macroglobulinemia (ISSWM)** IPROSWM ☐ Low risk (0-1 score points except age >65) ☐ High risk (3-5) ☐ Intermediate risk (score 2 or age >65 alone) ☐ Not evaluated
☐ Follicular lymphoma	**Grading** DISHGRD ☐ Grade I ☐ Grade II ☐ Grade IIIa ☐ Not evaluated **Prognostic score (FLIPI)** PROSCORE ☐ Low risk ☐ Intermediate risk ☐ High risk ☐ Not evaluated
☐ Primary cutaneous follicle centre lymphoma	
☐ Mantle cell lymphoma	**Grading** GRADETYP2 ☐ indolent ☐ classical ☐ pleomorphic ☐ blastoid ☐ Not evaluated **Prognostic score (MIPI)** PROSCORE ☐ Low risk ☐ Intermediate risk ☐ High risk ☐ Not evaluated PRINDXKI KI-67 (Proliferation index) __ __ % Positive ☐ Not evaluated
☐ Diffuse large B-cell lymphoma (DLBCL), (NOS) ☐ T-cell/hystiocyte rich large B cell lymphoma ☐ Primary DLBCL of the CNS ☐ Primary cutaneous DLBCL, leg type ☐ EBV positive DLBCL of the elderly ☐ DLBCL associated with chronic inflammation ☐ Lymphomatoid granulomatosis ☐ Primary mediastinal (thymic) large B-cell lymphoma ☐ Intravascular large B-cell lymphoma ☐ ALK positive large B-cell lymphoma ☐ Plasmablastic lymphoma ☐ Large B-cell lymphoma arising in HHV8- associated multicentric Castleman disease ☐ Primary effusion lymphoma (PEL) ☐ Burkitt lymphoma (BL) ☐ High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements ☐ High-grade B-cell lymphoma, NOS ☐ B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (Intermediate DLBCL/HD) ☐ Other B-cell, specify:_____ VDIAGTX	**International Prognostic Index (IPI)** IPROINDEX ☐ Low risk (0-1 score points) ☐ Low-Intermediate risk (2) ☐ High-intermediate risk (3) ☐ High risk (4 or 5) ☐ Not evaluated KI-67 (Proliferation index) __ __ % Positive ☐ Not evaluated PRINDXKI

Transformed from another type of lymphoma at the event leading to this Cellular Therapy? VSECORIG

☐ No

☐ Yes: Date of original diagnosis .... - .... - .... IDAABB

yyyy *mm* *dd*

Indicate the type of the original lymphoma .... WHOLYCLS

☐ Unknown

Selected B-Cell Non Hodgkin Lymphomas (NHL)

⇨ **Please complete this section for patients given treatment for the following types of B-cell NHL:**

- **Mantle cell lymphoma**
- **Waldenstrom macroglobulinaemia**
- **All DLBCL** (see list below)

All DLBCL, include:
- Diffuse large B-cell lymphoma (DLBCL), (NOS)
- T-cell/hystiocyte rich large B cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV positive DLBCL of the elderly
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8- associated multicentric Castleman disease
- Primary effusion lymphoma (PEL)
- Burkitt lymphoma (BL)
- High-grade B-cell lymphomas
- Intermediate DLBCL/HD

Chromosome Analysis at any time before CT

Chromosome / genetic analysis done? ☐ No *(skip this section)* ☐ Yes *(continue with this section)*

☐ Normal ☐ Abnormal ☐ Unknown VCHROMOS

If abnormal, please complete this table according to the type of lymphoma diagnosed IDAABECC CHROPRES FISHANA

	Abnormality	Absent	Present	FISH used	Not evaluated
Mantle cell lymphoma *or* Waldenstrom macroglobulinaemia	del 17p	☐	☐	☐ No ☐ Yes	☐
All DLBCL	t(2;8)	☐	☐	☐ No ☐ Yes	☐
	t(8;14)	☐	☐		☐
	t(8;22)	☐	☐		☐
	t(14;18)	☐	☐		☐
	myc rearrangement	☐	☐		☐
	BCL-2 rearrangement	☐	☐		☐
	BCL-6 rearrangement	☐	☐		☐

Molecular Markers at any time before CT

Molecular analysis done? ☐ No *(skip to the next section)* ☐ Yes *(continue with the next question)*

☐ Present ☐ Absent ☐ Unknown MOLEBIO

IDAABECL MOLPRES

Provide answers according to the type of lymphoma diagnosed

	Marker	Present	Absent	Not evaluated
Mantle cell lymphoma	TP53 mutation	☐	☐	☐
All DLBCL	*myc* rearrangement	☐	☐	☐
	BCL-2 rearrangement	☐	☐	☐
	BCL-6 rearrangement	☐	☐	☐

Immunophenotyping / immunohistochemistry at any time before CT

Immunophenotyping tested ☐ Yes ☐ No ☐ Unknown

Provide answers according to the type of lymphoma diagnosed VIMMUNOP IDAABECB IMMNDONE

	Phenotype	Present	Absent	Not evaluated
Mantle cell lymphoma	SOX11	☐	☐	☐
All DLBCL	MYC	☐	☐	☐
	BCL-2	☐	☐	☐
	BCL-6	☐	☐	☐

LYMPHOMAS
T-Cell Non Hodgkin Lymphomas (NHL) (main disease code 3)

Disease

Mature T-cell & NK-cell Neoplasms WHOLYCLS

Complete only for corresponding classifications from the left side

- ☐ T-cell large granular lymphocytic leukaemia
- ☐ Aggressive NK-cell leukaemia
- ☐ Systemic EBV positive T-cell lymphoproliferative disease of childhood
- ☐ Hydroa vacciniforme-like lymphoma
- ☐ Adult T-cell leukaemia/lymphoma
- ☐ Extranodal NK/T-cell lymphoma, nasal type
- ☐ Enteropathy-associated T-cell lymphoma
- ☐ Monomorphic epitheliotropic intestinal T-cell lymphoma
- ☐ Intestinal T-cell lymphoma NOS
- ☐ Hepatosplenic T-cell lymphoma
- ☐ Subcutaneous panniculitis-like T-cell lymphoma
- ☐ Mycosis fungoides (MF)
- ☐ Sézary syndrome

ISCL/EORTC STAGE STAGE

☐ IA ☐ IB ☐ IIA ☐ IIB ☐ IIIA ☐ IIIB ☐ IVA1 ☐ IVA2 ☐ IVB ☐ Not evaluated

- ☐ Lymphomatoid papulosis
- ☐ Primary cutaneous anaplastic large cell lymphoma
- ☐ Primary cutaneous gamma-delta T-cell lymphoma
- ☐ Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma
- ☐ Primary cutaneous CD4 positive small/medium T-cell lymphoma
- ☐ Peripheral T-cell lymphoma, NOS (PTCL)
- ☐ Angioimmunoblastic T-cell lymphoma
- ☐ Anaplastic large-cell lymphoma (ALCL), ALK-positive
- ☐ Anaplastic large-cell lymphoma (ALCL), ALK-negative
- ☐ Other T-cell, specify:_____ VDIAGTX

International Prognostic Index (IPI) IPROINDEX

- ☐ Low risk (0-1 score points)
- ☐ Low-Intermediate risk (2)
- ☐ High-intermediate risk (3)
- ☐ High risk (4 or 5)
- ☐ Not evaluated

LYMPHOMAS
Hodgkin Lymphomas (main disease code 3)

Classification: WHOLYCLS HODGKIN

- ☐ Nodular lymphocyte predominant
- ☐ Classical predominant
- ☐ Other, specify:_____ VDIAGTX

LYMPHOMAS
Immunodeficiency-associated lymphoproliferative disorders (including PTLD)
(main disease code 3)

Classification: WHOLYCLS

- ☐ Lymphoproliferative disease associated with primary immune disorder
- ☐ Lymphoma associated with HIV infection
- ☐ Post-transplant lymphoproliferative disorder (PTLD)
  - ☐ Non-destructive PTLD
    - ☐ Plasmacytic hyperplasia PTLD
    - ☐ Infectious mononucleosis PTLD
    - ☐ Florid follicular hyperplasia PTLD
  - ☐ Polymorphic PTLD
  - ☐ Monomorphic PTLD:
    - Cell type: ☐ B-cell type ☐ T-/NK-cell type
  - ☐ Classical Hodgkin lymphoma PTLD
- ☐ Other iatrogenic immunodeficiency-associated lymphoproliferative disorders

Did the disease result from a previous solid organ transplant? PREVORGTRAN

☐ No ☐ Yes:

Date of the transplant: ..... - ..... - ..... DATEORGANT
yyy mm dd

Type of transplant: ☐ Renal ☐ Cardiac ☐ Pulmonary ☐ Other, specify……..
TYPEORGTRAN OTHORGTRAN

ALL LYMPHOMAS

Status at Cellular Therapy

Technique used for disease assessment:

CT scan done ☐ No ☐ Yes VCTSCAND

PET ☐ Negative ☐ Positive ☐ Not evaluated VPETSTAT

STATUS VDISESTA

- ☐ Never treated
- ☐ Complete remission (CR) VCRCONFI
  - ☐ Unconfirmed (CRU*) ☐ Confirmed
  - *CRU – complete response with persistent scan abnormalities of unknown significance
- ☐ Partial response (PR) – (with or without a prior CR)
- ☐ Stable disease
- ☐ Untreated relapse (from a previous CR) / untreated progression (from a previous PR) *
- ☐ Chemorefractory relapse or progression, including primary refractory disease *
- ☐ Not Evaluable
- ☐ Not Evaluated

* Answer additional Histopathological verification question below

For **Relapse** status only:
Histopathological verification of relapse? ☐ No ☐ Yes HISTPATHOLYM

Was this patient **refractory** to any line of chemotherapy before this Cellular Therapy? ☐ No ☐ Yes REFRPAST

Number of Complete remissions (CR, CRu) achieved by the patient prior to this Cellular Therapy: …….. NBRCRBG
Count all CR including this one if applicable

Number of Partial remissions (PR) achieved by the patient prior to this Cellular Therapy: …….. NCRCRUPR
Count all PR including this one if applicable

Number of prior lines of treatment ☐ 1 ☐ 2 ☐ 3 or more ☐ None ☐ unknown TOTNTHER
(since diagnosis if 1st main treatment, or since last reported main treatment)

MYELODYSPLASTIC SYNDROME (MDS) (main disease code 6)

Disease

VMDSMPS
Select only one
WHO Classification at diagnosis: MDSSTAG

- ☐ Refractory anaemia (RA) *(without ring sideroblasts)*
- ☐ RA with ring sideroblasts (RARS)
- ☐ MDS associated with isolated del(5q)
- ☐ Refractory cytopenia with multilineage dysplasia (RCMD)
- ☐ RCMD with ringed sideroblasts (RCMD-RS)
- ☐ RA with excess of blasts-1 (RAEB-1)
- ☐ RA with excess of blasts-2 (RAEB-2)
- ☐ Childhood myelodysplastic syndrome (*Refractory cytopenia of childhood (RCC)*)
- ☐ MDS Unclassifiable (MDS-U)

Secondary Origin?

Therapy related MDS:
(Secondary origin)

- ☐ Yes: Disease related to prior exposure to therapeutic drugs or radiation
- ☐ No
- ☐ Unknown VSECORIG

IF THE PATIENT HAS RECEIVED AN ALLOGRAFT TREATMENT PRIOR TO THE DIAGNOSIS OF ACUTE LEUKAEMIA, ANSWER THE FOLLOWING QUESTION

Is this a donor cell leukaemia ☐ No ☐ Yes ☐ Not evaluated ☐ Unknown
RPDRGRAD

MYELODYSPLASTIC SYNDROME (MDS) (main disease code 6)

CYTOGENETICS DATA

(INCLUDE ALL ANALYSIS BEFORE TREATMENT; DESCRIBE RESULTS OF MOST RECENT COMPLETE ANALYSIS)

Chromosome / genetic analysis done? ☐ No *(skip to MOLECULAR MARKERS)* ☐ Yes *(continue with the next questions)*

Chromosome analysis at diagnosis (All methods including FISH) VCHROMOS

☐ Normal

☐ Abnormal:

MORE3AB **Complex karyotype:** ☐ No ☐ Yes ☐ Unknown
(3 or more abnormalities)

☐ Unknown

CHRMABND

You can transcribe the complete karyotype: .....

OR

Indicate below those abnormalities that have been **evaluated** and whether they were **Absent** or **Present** IDAABECC

del Y *(-Y)*	☐ Absent	☐ Present	☐ Not evaluated
abn 5 type *Fill only if* abn 5 *is Present:*	☐ Absent	☐ Present	☐ Not evaluated
del5q *(5q-)*	☐ Absent	☐ Present	☐ Not evaluated
Other abn 5, specify ……	☐ Absent	☐ Present	☐ Not evaluated
del 20q *(20q-)*	☐ Absent	☐ Present	☐ Not evaluated
abn 7 type *Fill only if* abn 7 *is Present:*	☐ Absent	☐ Present	☐ Not evaluated
del 7q (7q-)	☐ Absent	☐ Present	☐ Not evaluated
Other abn 7, specify ……	☐ Absent	☐ Present	☐ Not evaluated
abn 3 type *Fill only if* abn 3 *is Present:*	☐ Absent	☐ Present	☐ Not evaluated
inv(3)	☐ Absent	☐ Present	☐ Not evaluated
t(3q;3q)	☐ Absent	☐ Present	☐ Not evaluated
del(3q)	☐ Absent	☐ Present	☐ Not evaluated
Other abn 3, specify ……	☐ Absent	☐ Present	☐ Not evaluated
del11q	☐ Absent	☐ Present	☐ Not evaluated
trisomy 8	☐ Absent	☐ Present	☐ Not evaluated
trisomy 19	☐ Absent	☐ Present	☐ Not evaluated
i(17q)	☐ Absent	☐ Present	☐ Not evaluated
Other, specify	☐ Absent	☐ Present	☐ Not evaluated

MOLECULAR MARKERS AT DIAGNOSIS

Molecula analysis done? ☐ No *(skip next question)* ☐ Yes *(continue with the next question)*

Marker analysis at diagnosis

☐ Absent ☐ Present ☐ Unknown

MOLEBIO

*If you are entering an **AML with myelodyplasia related changes,** return to the Acute Leukaemia (page 8) to continue*

MYELODYSPLASTIC SYNDROME (MDS) (main disease code 6)

Status at Cellular Therapy

Select only one

WHO Classification at time of this treatment: **MDSSTAG**

- ☐ Refractory anaemia (without ring sideroblasts) RA
- ☐ RA with ring sideroblasts (RARS)
- ☐ MDS associated with isolated del(5q)
- ☐ Refractory cytopenia with multilineage dysplasia (RCMD)
- ☐ RCMD with ringed sideroblasts (RCMD-RS)
- ☐ RA with excess of blasts-1 (RAEB-1)
- ☐ RA with excess of blasts-2 (RAEB-2)
- ☐ Childhood myelodysplastic syndrome (*Refractory cytopenia of childhood (RCC)*)
- ☐ MDS Unclassifiable (MDS-U)

STATUS VDISESTA	NUMBER VNUMSTM
Treated with chemotherapy: ☐ Primary refractory phase (no change)	
☐ Complete remission (CR)	☐ 1st ☐ 2nd ☐ 3rd or higher
☐ Improvement but no CR	
☐ Relapse (after CR)	☐ 1st ☐ 2nd ☐ 3rd or higher
☐ Progression/worse ☐ Never treated (Supportive care or treatment without chemotherapy)	

COMBINED MYELODYSPLASTIC SYNDROME/MYELOPROLIFERATIVE NEOPLASM (MDS/MPN) (main disease code 6)

Disease

VMDSMPS MDSAMPS

- ☐ Chronic myelomonocytic leukaemia (CMMoL, CMML)
- ☐ Juvenile myelomonocytic leukaemia (JCMMoL, JMML, JCML, JCMML)
- ☐ Atypical CML ((t(9;22) negative and BCR-ABL1 negative)

Therapy related MDS/MPN: *(Secondary origin)*

- ☐ Yes: Disease related to prior exposure to therapeutic drugs or radiation
- ☐ No
- ☐ Unknown VSECORIG

CYTOGENETICS AND MOLECULAR MARKERS AT DIAGNOSIS

(INCLUDE ALL ANALYSIS BEFORE TREATMENT; DESCRIBE RESULTS OF MOST RECENT COMPLETE ANALYSIS)

Chromosome / genetic analysis done? ☐ No *(skip to MOLECULAR MARKERS)* ☐ Yes *(continue with the next question)*

Chromosome analysis (All methods including FISH) VCHROMOS

- ☐ Normal
- ☐ Abnormal:

MORE3AB **Complex karyotype:** *(3 or more abnormalities)* ☐ No ☐ Yes ☐ Unknown

☐ Unknown

You can transcribe the complete karyotype: .....

CHRMABND **OR**

Indicate below those abnormalities that have been **evaluated** and whether they were **Absent** or **Present** IDAABECC

CHROPRES

Abn 1, specify	☐ Absent	☐ Present	☐ Not evaluated
Abn 5, specify	☐ Absent	☐ Present	☐ Not evaluated
Abn 7, specify	☐ Absent	☐ Present	☐ Not evaluated
trisomy 8	☐ Absent	☐ Present	☐ Not evaluated
trisomy 9	☐ Absent	☐ Present	☐ Not evaluated
Del 20	☐ Absent	☐ Present	☐ Not evaluated
Del 13	☐ Absent	☐ Present	☐ Not evaluated
Other, specify	☐ Absent	☐ Present	☐ Not evaluated

MOLECULAR MARKERS

Molecula analysis done? ☐ No *(skip this section)* ☐ Yes *(continue with the next question)*

MOLEBIO

☐ Absent ☐ Present ☐ Unknown

IDAABECL MOLPRES

Indicate below those markers that have been **evaluated** and whether they were **Absent** or **Present**

BCR-ABL; *molecular product of t(9;22)(q34;q11.2)*	☐ Absent	☐ Present	☐ Not evaluated
JAK2 mutation	☐ Absent	☐ Present	☐ Not evaluated
FIP1L1-PDGFR	☐ Absent	☐ Present	☐ Not evaluated
PTPN-11	☐ Absent	☐ Present	☐ Not evaluated
K-RAS	☐ Absent	☐ Present	☐ Not evaluated
N-RAS	☐ Absent	☐ Present	☐ Not evaluated
CBL	☐ Absent	☐ Present	☐ Not evaluated
Other, specify.....	☐ Absent	☐ Present	☐ Not evaluated

COMBINED MYELODYSPLASTIC SYNDROME/MYELOPROLIFERATIVE NEOPLASM (MDS/MPN) (main disease code 6)

Status at Cellular Therapy

WHO Classification at time of this treatment: MDMPSTAG

- ☐ Chronic myelomonocytic leukaemia (CMMoL, CMML)
- ☐ Juvenile myelomonocytic leukaemia (JCMMoL, JMML, JCML, JCMML)
- ☐ Atypical CML ((t(9;22) negative and BCR-ABL1 negative)

STATUS
CMML / Atypical CML

STATUS VDISESTA	NUMBER VNUMSTM
Treated with chemotherapy: ☐ Primary refractory phase (no change)	
☐ Complete remission (CR)	☐ 1st ☐ 2nd ☐ 3rd or higher
☐ Improvement but no CR	
☐ Relapse (after CR)	☐ 1st ☐ 2nd ☐ 3rd or higher
☐ Progression/worse ☐ Never treated (Supportive care or treatment without chemotherapy)	

MYELOPROLIFERATIVE NEOPLASMS (MPN) (main disease code 6)

Disease

VMDSMPS VMPS

- ☐ Primary myelofibrosis *(Chronic idiopathic myelofibrosis; fibrosis with myeloid metaplasia)*
- ☐ Polycythaemia vera
- ☐ Essential or primary thrombocythaemia
- ☐ Hyper eosinophilic syndrome (HES)
- ☐ Chronic eosinophilic leukaemia (CEL)
- ☐ Chronic neutrophilic leukaemia
- ☐ Systemic mastocytosis
- ☐ Mast cell leukaemia
- ☐ Mast cell sarcoma
- ☐ MPN not otherwise specified
- ☐ Myeloid and lymphoid neoplasms with FGFR1 abnormalities *(Stem cell leukaemia-lymphoma syndrome, 8p11 syndrome)*

Secondary origin: ☐ Yes: Disease related to prior exposure to therapeutic drugs or radiation
☐ No
☐ Unknown VSECORIG

IPSS Risk score for Myelofibrosis IPSSRSC
☐ Low risk ☐ Intermediate-1 ☐ Intermediate-2 ☐ High risk ☐ Not evaluated

CYTOGENETICS AND MOLECULAR MARKERS AT DIAGNOSIS

(INCLUDE ALL ANALYSIS BEFORE TREATMENT; DESCRIBE RESULTS OF MOST RECENT COMPLETE ANALYSIS)

Chromosome / genetic analysis done? ☐ No *(skip to MOLECULAR MARKERS)* ☐ Yes *(continue with the next question)*

Chromosome analysis (All methods including FISH) VCHROMOS
☐ Normal
☐ Abnormal
Complex karyotype: ☐ No ☐ Yes ☐ Unknown

☐ Unknown

You can transcribe the complete karyotype: .....

ARYO_YN CHRMABND **OR**

Indicate below those abnormalities that have been **evaluated** and whether they were **Absent** or **Present** IDAABECC CHROPRES

Abn 1, specify	☐ Absent	☐ Present	☐ Not evaluated
Abn 5, specify.....	☐ Absent	☐ Present	☐ Not evaluated
Abn 7, specify	☐ Absent	☐ Present	☐ Not evaluated
trisomy 8	☐ Absent	☐ Present	☐ Not evaluated
trisomy 9	☐ Absent	☐ Present	☐ Not evaluated
Del 20	☐ Absent	☐ Present	☐ Not evaluated
Del 13	☐ Absent	☐ Present	☐ Not evaluated
Other, specify	☐ Absent	☐ Present	☐ Not evaluated

Molecular markers at diagnosis MOLEBIO

Molecula analysis done? ☐ No *(skip this section)* ☐ Yes *(continue with the next question)*
☐ Absent ☐ Present ☐ Unknown

IDAABECL MOLPRES

Indicate below those markers that have been **evaluated** and whether they were **Absent** or **Present**

BCR-ABL	☐ Absent	☐ Present	☐ Not evaluated	
JAK2 mutation	☐ Absent	☐ Present	☐ Not evaluated	If present: Allele burden % ..... MKRPERCT
cMPL mutation	☐ Absent	☐ Present	☐ Not evaluated	
Cal Reticulin mutation	☐ Absent	☐ Present	☐ Not evaluated	
FIP1L1-PDGFR	☐ Absent	☐ Present	☐ Not evaluated	
Other, specify.....	☐ Absent	☐ Present	☐ Not evaluated	

MYELOPROLIFERATIVE NEOPLASMS (MPN) (main disease code 6)

Status at Cellular Therapy

Classification at time of this treatment: VMPS

- ☐ Primary myelofibrosis *(Chronic idiopathic myelofibrosis; fibrosis with myeloid metaplasia)*
- ☐ Polycythaemia vera
- ☐ Essential or primary thrombocythaemia
- ☐ Hyper eosinophilic syndrome (HES)
- ☐ Chronic eosinophilic leukaemia (CEL)
- ☐ Chronic neutrophilic leukaemia
- ☐ Systemic mastocytosis
- ☐ Mast cell leukaemia
- ☐ Mast cell sarcoma

- ☐ Myeloid and lymphoid neoplasms with FGFR1 abnormalities *(Stem cell leukaemia-lymphoma syndrome, 8p11 syndrome)*

- ☐ Transformed to myelofibrosis from PV/ET: Date of transformation ..... - ..... - ..... DATTRAN
  yyyy mm dd
- ☐ Transformed to AML
- ☐ MPN not otherwise specified

DIPSS Risk score for Myelofibrosis DIPSSRSC

☐ Low risk ☐ Intermediate-1 ☐ Intermediate-2 ☐ High risk ☐ Not evaluated

STATUS VDISESTA	NUMBER VNUMSTM
Treated with chemotherapy: ☐ Primary refractory phase (no change)	
☐ Complete remission (CR)	☐ 1st ☐ 2nd ☐ 3rd or higher
☐ Improvement but no CR	
☐ Relapse (after CR)	☐ 1st ☐ 2nd ☐ 3rd or higher
☐ Progression/worse ☐ Never treated (Supportive care or treatment without chemotherapy)	

PLASMA CELL DISORDERS (PCD) including MULTIPLE MYELOMA (MM) (main disease code 4)

Disease

Classification VPLCEDS1

- ☐ Multiple myeloma (MM) VPLCEDS3
  - ☐ MM –heavy chain and light chain *Check light and heavy chain types →*
  - ☐ MM -light chain *Check light chain type only →*
  - ☐ MM -non-secretory
- ☐ Plasma cell leukaemia
- ☐ Solitary plasmacytoma of bone
- ☐ Primary amyloidosis
- ☐ POEMS
- ☐ Monoclonal light and heavy chain deposition disease (LCDD/HCDD)
- ☐ Other

VPLCEDS2 **IG TYPE**
- ☐ IgG
- ☐ IgA
- ☐ IgD
- ☐ IgE
- ☐ IgM *(not Waldenstrom)*

VPLCEDS4 **LIGHT CHAIN TYPE**
- ☐ Kappa
- ☐ Lambda

STAGE AT DIAGNOSIS VSTGDST
Complete both staging systems

SALMON AND DURIE (MM)

	I	II	III
A	☐	☐	☐
B	☐	☐	☐

VSALMDUR

REVISED ISS RISS

- ☐ **I** ISS I without high risk FISH and normal LDH
- ☐ **II** not R-ISS I or III
- ☐ **III** any ISS with high risk FISH and/or high LDH

or **ISS** ISS

	β2 µglob *(mg/L)*	Albumin *(g/L)*		β2 µglob *(mg/L)*	Albumin *(g/L)*
☐ **I**	<3.5	≥35			
☐ **II**	<3.5	<35	***OR***	3.5 – ≤5.5	any
☐ **III**	>5.5	any			

Chromosome analysis at diagnosis (All methods including FISH) VCHROMOS
Not for Primary amyloidosis

Chromosome / genetic analysis done? ☐ No *(skip to MOLECULAR MARKERS)* ☐ Yes *(continue with the next question)*

☐ Normal

☐ Unknown

☐ Abnormal: VCHROMOS
Complex karyotype: ☐ No ☐ Yes ☐ Unknown
(3 or more abnormalities) MORE3AB

You can transcribe the complete karyotype: .....

CHRMABND **OR**

Indicate below those abnormalities that have been **evaluated** and whether they were **Absent** or **Present**

If abnormal, indicate abnormalities found: IDAABECC CHROPRES

Del 13q14	☐ Absent	☐ Present	☐ Not evaluated
t(11;14)	☐ Absent	☐ Present	☐ Not evaluated
abn 17q	☐ Absent	☐ Present	☐ Not evaluated
17p del	☐ Absent	☐ Present	☐ Not evaluated
t(4:14)	☐ Absent	☐ Present	☐ Not evaluated
t(14:16)	☐ Absent	☐ Present	☐ Not evaluated
1q amplification	☐ Absent	☐ Present	☐ Not evaluated
myc rearrangement	☐ Absent	☐ Present	☐ Not evaluated
Other, specify	☐ Absent	☐ Present	☐ Not evaluated

☐ Other or associated abnormalities (specify).....

PLASMA CELL DISORDERS (PCD) including MULTIPLE MYELOMA (MM) (main disease code 4)

Molecular analysis
Not for Primary amyloidosis

Molecular analysis done? ☐ No *(skip the next question)* ☐ Yes *(continue with the next question)*

MOLEBIO ☐ Absent ☐ Present (at least one) ☐ Unknown

Status at Cellular Therapy

STATUS VDISESTA	NUMBER VNUMSTM
☐ Never treated	
☐ Stringent complete remission (sCR) ☐ Complete remission (CR) ☐ Very good partial remission (VGPR) ☐ Partial remission (PR) ☐ Relapse from CR (untreated)	☐ 1st ☐ 2nd ☐ 3rd or higher
☐ Progression ☐ No change / stable disease	

BONE MARROW FAILURE SYNDROMES (BMF) including APLASTIC ANAEMIA (AA) (main disease code 7)

Disease

Classification: BMFTYPE BMFSACQ

Acquired:

- ☐ Severe Aplastic Anaemia (SAA),
- ☐ Amegakaryocytosis, acquired (not congenital)
- ☐ Acquired Pure Red Cell Aplasia (PRCA) (not congenital)
- ☐ Paroxysmal nocturnal haemoglobinuria (PNH)
- ☐ Acquired Pure White Cell Aplasia
- ☐ Other acquired cytopenic syndrome, specify: _____ VDIAGTX

ACQBMFE Etiology:

- ☐ Secondary to hepatitis
- ☐ Secondary to toxin/other drug
- ☐ Idiopathic
- ☐ Other, specify: _____ VOTHSAEE

Congenital: BMFTYPE BMFSGEN

- ☐ Amegakaryocytosis / thrombocytopenia
- ☐ Fanconi anaemia
- ☐ Diamond-Blackfan anaemia (congenital PRCA)
- ☐ Shwachman-Diamond Syndrome
- ☐ Dyserythropoietic anaemia
- ☐ Dyskeratoris congenita
- ☐ Other congenital anaemia, specify: _____ VDIAGTX

HAEMOGLOBINOPATHY (main disease code 11)

Disease

Classification: VHEMOGLO

☐ Thalassaemia: ☐Beta 0 ☐Beta + ☐Beta E THALTYPE ☐Beta S (sickle cell + thalassaemia)
% sickle cell = ... VSICKLPC

☐ Sickle cell disease

☐ Other haemoglobinopathy, specify: _____ VDIAGTX

SOLID TUMOURS (main disease code 5)

Disease

Classification: VSOLTUMO

- ☐ Bone sarcoma (excluding Ewing sarcoma/PNET)
- ☐ Breast
- ☐ Central nervous system tumours (include CNS PNET)
- ☐ Colorectal
- ☐ Ewing sarcoma (ES)/PNET, extra-skeletal
- ☐ Ewing sarcoma(ES)/PNET, skeletal
- ☐ Germ cell tumour, extragonadal only
- ☐ Head and neck
- ☐ Hepatobiliary
- ☐ Kidney cancer excluding Wilm's tumour
- ☐ Lung cancer, non-small cell
- ☐ Lung cancer, small cell
- ☐ Medulloblastoma
- ☐ Melanoma
- ☐ Other, specify ..... VDIAGTX
- ☐ Neuroblastoma
- ☐ Ovarian (carcinoma)
- ☐ Pancreatic
- ☐ Prostate
- ☐ Renal cell
- ☐ Retinoblastoma
- ☐ Rhabdomyosarcoma
- ☐ Soft tissue sarcoma (excluding Rhabdo. and extra-skeletal ES)
- ☐ Germ cell tumour, gonadal
- ☐ Thymoma
- ☐ Wilm's tumour

TNM classification

Type: ☐ Clinical ☐ Pathological VTNMTYPE

	0	1	2	3	4	X	Not evaluated	Unknown
Tumour	☐	☐	☐	☐	☐	☐	☐	☐ VTNMT
Nodes	☐	☐	☐	☐		☐	☐	☐ VTNMN
Metastases*	☐	☐				☐	☐	☐ VTNMM

*For metastases, 0 indicates "No metastasis", 1 indicates "Metastasis" and X indicates "Not evaluable"

Disease-specific staging I ☐ II ☐ III ☐ IV ☐ Not evaluated ☐ Unknown ☐ VSTGDST

BREAST CARCINOMA ONLY

RECEPTOR STATUS

Estrogen (ER): ☐ Negative ☐ Positive ☐ Not evaluated VESTROGR VESRCVAL if Positive, ER values .....

Progesterone (PgR): ☐ Negative ☐ Positive ☐ Not evaluated VPROGESR VPRGRCVA if Positive, PgR values .....

HER2/neu (c-erb-B2): ☐ Negative ☐ Positive HER2EUR ☐ Not evaluated

Defined by: ☐ IHC 3+ ☐ IHC 1/2+ and FISH+ HER2DEF

HISTOLOGICAL SUBCLASSIFICATION

Axillary lymph nodes at surgery: N° examined: .... / N° positive:..... .... ☐ Not evaluated
VNISOBRC VNINVBRC

Sentinel Node ☐ Negative ☐ Positive ☐ Not evaluated SNTNLNDG

Carcinoma type *(tick only one)*

☐ Ductal carcinoma ☐ Lobular carcinoma VDUCTALC VLOBULAR

Proliferation index (activity by Ki67 or MiB1 immunostaining) (% of positive cells) ..... PRINDXKI

GERM CELL TUMOURS ONLY

Histological classification VHSTCLAS

☐ Seminoma ☐ Non-seminoma

Site of origin VBGFGRCT

☐ Gonadal

☐ Extragonadal: ☐ retroperitoneal ☐ mediastinal ☐ other sites (specify) ..... VBGFGRCT

Status at Cellular Therapy

GERM CELL TUMOURS

Risk category at disease recurrence (or platinum refractoriness) following first line CT GRMCLRSC

☐ Very Low ☐ Low ☐ Intermediate ☐ High ☐ Very High ☐ Not evaluated

STATUS VDISESTA

☐ Adjuvant
☐ Never treated (upfront)
☐ Stable disease/no response

☐ Complete remission (CR) VCRCONFI ☐ Confirmed ☐ Unconfirmed (CRU*) *CRU – complete response with persistent scan abnormalities of unknown significance	NUMBER VNUMSTM ☐ 1st ☐ 2nd ☐ 3rd or higher	
☐ 1st Partial response (PR1)		
☐ Relapse	NUMBER VNUMSTM ☐ 1st ☐ 2nd ☐ 3rd or higher	SENSITIVITY TO CHEMOTHERAPY ☐ Sensitive ☐ Resistant ☐ Untreated VSENSIT
☐ Progressive disease (PD)		

Organ(s) involved (*complete only if not in CR***)** IDAABECK

☐ Nodes Below Diaphragm
☐ Bone
☐ Lungs
☐ Soft Tissue
☐ Other: ..... ORGANOTS

☐ Nodes Above Diaphragm
☐ CNS
☐ Liver

PRIMARY IMMUNE DEFICIENCIES (PID) (main disease code 8)

Disease

Classification: INHDIS IMMDEF

- ☐ Absence of T and B cells SCID
- ☐ Absence of T, normal B cell SCID
- ☐ ADA deficiency (Adenosine deaminase deficiency)
- ☐ Ataxia telangiectasia
- ☐ Bare lymphocyte syndrome
- ☐ Cartilage hair hypoplasia
- ☐ CD 40 Ligand deficiency
- ☐ Chediak-Higashi syndrome
- ☐ Chronic granulomatous disease
- ☐ Common variable immunodeficiency
- ☐ DiGeorge anomaly
- ☐ Immune deficiencies, not otherwise specified
- ☐ Kostmann syndrome-congenital neutropenia
- ☐ Leukocyte adhesion deficiencies
- ☐ Neutrophil actin deficiency
- ☐ Omenn syndrome
- ☐ PNP deficiency *(Purine nucleoside phosphorylase)*
- ☐ Reticular dysgenesis
- ☐ SCID other, specify: ..... VDIAGTX
- ☐ SCID, unspecified
- ☐ Wiskott Aldrich syndrome
- ☐ X-linked lymphoproliferative syndrome
- ☐ Other, specify: .....VDIAGTX

INHERITED DISORDERS OF METABOLISM (main disease code 8)

Disease

Classification: INHDIS VINBERR2

- ☐ Adrenoleukodystrophy
- ☐ Aspartyl glucosaminuria
- ☐ B-glucuronidase deficiency (VII)
- ☐ Fucosidosis
- ☐ Gaucher disease
- ☐ Glucose storage disease
- ☐ Hunter syndrome (II)
- ☐ Hurler syndrome (IH)
- ☐ I-cell disease
- ☐ Krabbe disease (globoid leukodystrophy)
- ☐ Lesch-Nyhan (HGPRT deficiency)
- ☐ Mannosidosis
- ☐ Maroteaux-Lamy (VI)
- ☐ Metachromatic leukodystrophy
- ☐ Morquio (IV)
- ☐ Mucolipidoses, unspecified
- ☐ Mucopolysaccharidosis (V)
- ☐ Mucopolysaccharidosis, unspecified
- ☐ Niemann-Pick disease (Type A,B)
- ☐ Niemann-Pick disease (Type C,D,E)
- ☐ Neuronal ceroid – lipofuscinosis (Batten disease)
- ☐ Polysaccharide hydrolase abnormalities, unspecified
- ☐ Sanfilippo (III)
- ☐ Scheie syndrome (IS)
- ☐ Wolman disease
- ☐ Other, specify: ..... VDIAGTX
- ☐ Inherited disorders of metabolism, not otherwise specified

PLATELET and OTHER INHERITED DISORDERS (main disease code 8)

Disease

Classification: VINBERR3

- ☐ Glanzmann thrombasthenia
- ☐ Other inherited platelet abnormalities, unspecified

- ☐ Osteopetrosis (malignant infantile osteopetrosis)
- ☐ Other osteoclast defects, unspecified

HISTIOCYTIC DISORDERS (main disease code 9)

Disease

Classification: HISTIOCY

- ☐ Histiocytic disorders, not otherwise specified
- ☐ Familial erythro/haemophagocytic lymphohistiocytosis (FELH)
- ☐ Langerhans Cell Histiocytosis *(Histiocytosis-X)*
- ☐ Haemophagocytosis (reactive or viral associated)
- ☐ Histiocytic sarcoma *(malignant histiocytosis)*
- ☐ Other, specify:_____ VDIAGTX

AUTOIMMUNE DISORDERS (main disease code 10)

CONNECTIVE TISSUE

DISEASE

Classification: VAUTOIM1

☐ Systemic sclerosis (SS) VAUTOIM2

Involvement/Clinical problem SSCUTEXT

- ☐ diffuse cutaneous
- ☐ limited cutaneous
- ☐ SSc sine scleroderma
- ☐ Other (MCTD: Mixed Connective Tissue Disease)
- ☐ other, specify:_____ SSCINVOT

☐ Systemic lupus erythematosus (SLE) VAUTOIM2

☐ Polymyositis- dermatomyositis VAUTOIM1

☐ Sjögren syndrome

☐ Antiphospholipid syndrome

☐ Other type of connective tisue disease, specify:_____ VDIAGTX VAUTOIM2

VASCULITIS VAUTOIM1

DISEASE

Classification: VAUTOIM3

☐ Wegener granulomatosis

☐ Classical polyarteritis nodosa

☐ Microscopic polyarteritis nodosa

☐ Churg-Strauss

☐ Giant cell arteritis

☐ Takayasu

☐ Behçet's syndrome

☐ Overlap necrotising arteritis

☐ Other, specify:_____ VDIAGTX

AUTOIMMUNE DISORDERS cont. (main disease code 10)

ARTHRITIS VAUTOIM1

DISEASE

Classification: VAUTOIM4

- ☐ Rheumatoid arthritis
- ☐ Psoriatic arthritis/psoriasis
- ☐ Juvenile idiopathic arthritis (JIA), systemic (Stills disease)
- ☐ Juvenile idiopathic arthritis (JIA), articular: Onset ☐ Oligoarticular PRAONSET ☐ Polyarticular
- ☐ Juvenile idiopathic arthritis: other
- ☐ Other arthritis: ..... VDIAGTX

NEUROLOGICAL

DISEASE

Classification: VAUTOIM1

☐ MULTIPLE SCLEROSIS

☐ OTHER NEUROLOGICAL: VAUTOIM1 VAUTOIM5

- ☐ Myasthenia gravis
- ☐ Amyotrophic lateral sclerosis (ALS)
- ☐ Chronic inflammatory demyelinating polyneuropathy (CIDP)
- ☐ Neuromyelitis Optica (NMO)
- ☐ Other autoimmune neurological disorder, specify:_____ VDIAGTX

HAEMATOLOGICAL VAUTOIM1

DISEASE

Classification: VAUTOIM6

- ☐ Idiopathic thrombocytopenic purpura (ITP)
- ☐ Haemolytic anaemia
- ☐ Evan syndrome
- ☐ Autoimmune lymphoproliferative syndrome (primary diagnosis, not subsequent to transplant)
- ☐ Other haematological autoimmune disease, specify:_____ VDIAGTX

AUTOIMMUNE DISORDERS cont. (main disease code 10)

BOWEL VAUTOIM1

DISEASE

Classification: VAUTOIM7

- ☐ Crohn's disease
- ☐ Ulcerative colitis
- ☐ Other autoimmune bowel disease, specify:_____ VDIAGTX

OTHER AUTOIMMUNE DISORDER

DISEASE

Classification: VAUTOIM1

- ☐ Graves' disease
- ☐ Insulin dependent diabetes (IDD)
- ☐ Other autoimmune, specify:_____ VDIAGTX

OTHER PRIMARY DISEASE

NEUROLOGIC DISORDES (main disease code 12)

Classification:

- ☐ Duchenne Muscular Distrophy **NEURODIS**
- ☐ Acute cerebral vascular ischemia
- ☐ ALS, amiotrophic lateral sclerosis
- ☐ Parkinson disease
- ☐ Spinal cord injury
- ☐ Cerebral palsy
- ☐ Congenital hydrocephalus
- ☐ Other, specify:_____ **VDIAGTX**

HEART (CARDIOVASCULAR) DISEASE (main disease code 13)

Classification:

- ☐ Acute myocardial infarction (AMI) **CARDIODIS**
- ☐ Chronic coronary artery disease (ischemic, cardiomyopathy)
- ☐ Heart failure (non-ischemic etiology)
- ☐ Other cardiovascular disease
- ☐ Limb ischemia
- ☐ Thromboangitis obliterans
- ☐ Other peripheral vascular disease
- ☐ Other, specify:_____ **VDIAGTX**

MUSCULOSKELETAL (main disease code 15)

Classification:

- ☐ Avascular necrosis of femoral head **MUSCSKDIS**
- ☐ Osteoarthritis
- ☐ Osteogenesis imperfecta
- ☐ Traumatic joint injury
- ☐ Other, specify:_____ **VDIAGTX**

INFECTIONS (main disease code 14)

☐ Prevention / prophylaxis INFTRTAIM
☐ Treatment:

Pathogen involved:
☐ Adenovirus ☐ BK virus ☐ Cytomegalovius (CMV) INFTRTPATH
☐ Epstein-Barr virus ☐ Human herpex virus
☐ Human immunodeficiency virus (HIV) ☐ Other virus, specify ……..
☐ Candida ☐ Aspergillus ☐ Other fungal, specify ……..
☐ Other, specify …….. INFTRTPATOTH

Advanced Cellular Therapies Form

Day 0

EBMT Unique Identification Code (UIC) ..... ID.IDAA

CENTRE IDENTIFICATION

EBMT Centre Identification Code (CIC): .... CENTRNR

Unit: ..... UNIT

Contact person..... MEDNAME

PATIENT DATA

Date of this Report: ..... - ..... - .....
DATLSTRE *yyyy* *mm* *dd*

Hospital Unique Patient Number or Code (UPN): ..... UPN
Compulsory, registrations will not be accepted without this item. *All treatments performed in the same patient must be registered with the same patient identification number or code as this belongs to the patient and not to the treatment.*

Other type of patient identification codes ..... VDOSSIER
(Optional: This item is to be used by the centre to register a patient code for internal use as necessary)

Initials: ....._..... (first name(s) _family name(s)) GIVNAME FAMNAME

Date of Birth: ..... - ..... - ..... DATPATBD
yyyy *mm* dd

Sex: ☐ Male ☐ Female PATSEX
(at birth)

Previous therapies given before transplant/advanced cellular therapy

Has the information requested in this section been submitted with a previous HSCT/Advanced Cellular Therapy registration for this patient?

☐ Yes: go to page 47, *"Status at Cellular Therapy"*
☐ No: proceed with this section

Was the patient treated before this Cellular Therapy procedure? VPRETRAT

☐ No – *Proceed to page 47, STATUS AT CELLULAR THERAPY*
☐ Yes **Date started** .... - .... IDAABC *(repeat for each line of therpy)*
yyyy mm dd

Sequential number of this treatment: ..... VSEQNUMB
(counted from diagnosis)

☐ Unknown

Chemotherapy/Drugs ☐ No ☐ Yes ☐ Unknown VCHEMOTH

If yes: IDAABCCD NUMCYCL TRETSTAR VINTBTDE TUMRSA2

	Regimen/Drugs	**No. of cycles**	**Date started**	**Date ended**	**Response**
1st Line			..... - ..... - ..... *yyyy mm dd*	..... - ..... - ..... *yyyy mm dd*	☐ Complete remission ☐ Partial remission (> 50 %) ☐ No response (< 50 %) ☐ Relapse/progression ☐ Not evaluable ☐ Not evaluated
2nd Line			..... - ..... - ..... *yyyy mm dd*	..... - ..... - ..... *yyyy mm dd*	☐ Complete remission ☐ Partial remission (> 50 %) ☐ No response (< 50 %) ☐ Relapse/progression ☐ Not evaluable ☐ Not evaluated
3rd Line			..... - ..... - ..... *yyyy mm dd*	..... - ..... - ..... *yyyy mm dd*	☐ Complete remission ☐ Partial remission (> 50 %) ☐ No response (< 50 %) ☐ Relapse/progression ☐ Not evaluable ☐ Not evaluated
4th Line			..... - ..... - ..... *yyyy mm dd*	..... - ..... - ..... *yyyy mm dd*	☐ Complete remission ☐ Partial remission (> 50 %) ☐ No response (< 50 %) ☐ Relapse/progression ☐ Not evaluable ☐ Not evaluated

If there are more than 4 please add another copy of this page.

Enzyme replacement therapy ☐ No ☐ Yes ☐ Unknown
ENZYME

Radiotherapy ☐ No ☐ Yes ☐ Unknown
VRADIOTH

Other treatment ☐ No ☐ Yes, specify: ..... ☐ Unknown VOTHERT
VOTHERTS

STATUS AT CELLULAR THERAPY

IF THE THE CELLULAR THERAPY PRODUCT WAS INFUSED REPORT:
Date of the first cell infusion ..... - ..... - ..... IDAABE / IDAABC
yyyy mm dd

OTHERWISE, IF THE TREATMENT DIDN'T GO AHEAD REPORT:
Date of the last assessment..... - ..... - ..... IDAABE / IDAABC
yyyy mm dd

WAS THE CELL PRODUCT INFUSED DURING THIS TREATMENT OR PROCEDURE? CELLPROINF

☐ No: Reason why the treatment didn't take place: …….. REASNOCT
☐ Yes

Performance score of the patient at initiation of treatment PERFSYST KARNOFSK

SYSTEM USED *(choose only one)*:

☐ Karnofsky or ☐ Lansky: Score: ☐ 20 ☐ 30 ☐ 40 ☐ 50 ☐ 60 ☐ 70 ☐ 80 ☐ 90 ☐ 100
☐ ECOG: ECOG Score: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

PATIENT WEIGHT AT CELLULAR THERAPY (kg): ..... WEIGHTB

HEIGHT AT CELLULAR THERAPY(cm): ..... HEIGHT

Was B-Cell Aplasia present at the time of treatment? ☐ No ☐ Yes ☐ Not Evaluated BCELLAPLAS

If yes, report % (percentage) of B-Cells …….. BCELLPC

COMORBIDITY INDEX

Sorror et al., Blood, 2005 Oct 15; 106(8): 2912-2919: *http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1895304/*

Was there any ***clinically significant*** co-existing disease or organ impairment as listed below at time of patient assessment prior to the preparative regimen? ☐ No ☐ Yes, indicate each comorbidity below ☐ Not evaluated **COMORBID**

Comorbidity	Definitions	No	Yes	Not evaluated
Solid tumour, previously present **MALIGN**	Treated at any time point in the patient's past history, excluding non-melanoma skin cancer Indicate type …… ……..……..**MALIGNTXT**	☐	☐	☐
Inflammatory bowel disease **INBWDIS**	Crohn's disease or ulcerative colitis	☐	☐	☐
Rheumatologic **RHEUMAT**	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	☐	☐	☐
Infection **INFECPRE**	Requiring continuation of antimicrobial treatment after day 0	☐	☐	☐
Diabetes **TRTDEPDB**	Requiring treatment with insulin or oral hypoglycaemics but not diet alone	☐	☐	☐
Renal: moderate/severe **KIDNEYCO**	Serum creatinine > 2 mg/dL or >177 µmol/L, on dialysis, or prior renal transplantation	☐	☐	☐
Hepatic: mild **HEPATIC**	Chronic hepatitis, bilirubin between Upper Limit Normal (ULN) and 1.5 x the ULN, or AST/ALT between ULN and 2.5 × ULN	☐	☐	☐
moderate/ severe	Liver cirrhosis, bilirubin greater than 1.5 × ULN, or AST/ALT greater than 2.5 × ULN	☐	☐	☐
Arrhythmia **ARRYTHBL**	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	☐	☐	☐
Cardiac **CARDIAC**	Coronary artery disease, congestive heart failure, myocardial infarction, EF ≤ 50%, or shortening fraction in children (<28%)	☐	☐	☐
Cerebrovascular disease **STROKE**	Transient ischemic attack or cerebrovascular accident	☐	☐	☐
Heart valve disease **VALVE**	Except mitral valve prolapse	☐	☐	☐
Pulmonary: moderate **PULMONC**	DLco and/or FEV1 66-80% or dyspnoea on slight activity	☐	☐	☐
severe	DLco and/or FEV1 ≤ 65% or dyspnoea at rest or requiring oxygen	☐	☐	☐
Obesity **OBESITY**	Patients with a body mass index > 35 kg/m2	☐	☐	☐
Peptic ulcer **PEPTICU**	Requiring treatment	☐	☐	☐
Psychiatric disturbance **PSYCH**	Depression or anxiety requiring psychiatric consultation or treatment	☐	☐	☐

Specify other additional ***major*** clinical abnormalities not listed above and present prior to the preparative regimen:

……
……
…… **OTHCLIAB**

CELLULAR THERAPY INFUSION UNIT(S)

Is it planned to administer more than one cell infusion unit during this treatment

☐ No **MNYINFUSED**

☐ Yes: Number of different cell infusion units that will form part of this treatment ..... **NUMCINFUNIT**

Cellular Therapy Infusion Unit – Description and collection

If more than one cell infusion unit, replicate this section for each one of them

IDENTIFICATION

Name of the manufacturer .... ☐ **N/A** **NAMCTIMNFCD** **NAMCTIMNFSP**
Enter Hospital name if it isn't a commercial product

Unique ID of the product *(if applicable)* ..... **PRODUCTID**

Name of the product *(if applicable)* .... **NAMCTIPKGCD** **NAMCTIPKGSP**

Batch number *(if applicable)* ..... **CTIPKGBAT**

Identification of the Cell Infusion Unit given by the Centre .... **CTIUCID**
If there is only one cell infusion unit write '1'.

Is the infused Advanced Cellular Therapy product a commercial product? **COMMPROD** **CONSPECIF**

☐ Yes: Was the product use consistent with the specification? ☐ Yes ☐ No

☐ No

Cellular Therapy Infusion Unit – Manipulation

COMPLETE ONLY FOR NON-COMMERCIAL PRODUCTS

If more than one cell infusion unit, replicate this section for each one of them:

Identification of the Cell Infusion Unit given by the Centre .... CTIUCID

EX-VIVO MANIPULATION OF THE PRODUCTS CONTAINED IN THE CELLULAR THERAPY INFUSION UNIT CIEXVIMANI

- ☐ No -> Skip MANIPULATION section and go straight to THERAPY AND CELL INFUSION on page 52
- ☐ Yes -> Continue with MANIPULATION section below
- ☐ Unknown

MANIPULATION

Processing/Manufacturing Facility

Onsite, by local cell processing facility	☐ No	☐ Yes MANIONSLPF
Offsite, by a non commercial facility	☐ No	☐ Yes MANIOFSNCF
Offsite, by a commercial facility	☐ No	☐ Yes MANIOFSCF

GENE MANIPULATION

☐ No MANIGENE MANIGENTRN

☐ Yes: TYPE

Gene transfer ☐ No ☐ Yes: ☐ Retroviral vector GENTRNRETV

GENTRNLEN ☐ Lentiviral vector

GENTRNOTH ☐ Other vector, specify ..... TRNOTHSPC

Transgene (select all that apply)

☐ CAR, specify all targets ..... TRNGENCAR GENCARSPC

☐ Suicide gene, specify..... TRNGENSUG GENSUGSPC

TRNGENTCR GENTCRSPC ☐ TCR, specify all targets ..... / specify HLA element ..... GENTCRSPCH

☐ Other, specify ..... TRNGENOTH GENOTHSPC

MANIGENEDT Gene editing ☐ No ☐ Yes: Manipulated gene ☐ CCR5 GENEDTCR5

☐ Factor IX GENEDTFIX

☐ Factor VIII GENEDTFVII

☐ Other gene, specify .....GENEDTOTH EDTOTHSPC

Other ☐ No ☐ Yes, specify ..... MANIGENOTH MANIOTHSPC

MANIPULATION AIMS

Recognition of a specific target / antigen

☐ No RECGTARANT TARANTADNV TARANTBKV TARANTCYMV TARANTEBV TARANTHHV TARANTHIV

☐ Yes: TYPE *(check all that apply)*

☐ Viral ☐ Adenovirus ☐ BK virus ☐ Cytomegalovirus (CMV)

VIRALANTG ☐ Epstein-Barr virus ☐ Human herpes virus 6 ☐ Human immunodeficiency virus (HIV)

☐ Other virus, specify ..... TARANTOTH TRGANTSPC

☐ Fungal ☐ Candida ☐ Aspergillus TARANTCAN TARANTASP

FUNGANTG ☐ Other fungal, specify ..... TARANTOTF TRGANTSPF

☐ Tumour / cancer antigen(s), specify all..... TUMRCANANT CANCANTSPC

☐ Other target, specify ..... RECTRGTOTH RTRGOTHSPC

Was there a cell selection process?

☐ No CTIUSELECT

☐ Yes: Positive ☐ No ☐ Yes CTIUSELPOS

If Yes, specify cell type..... CTIUSELPOSSP

Negative ☐ No ☐ Yes CTIUSELNEG

Expansion

☐ No CTIUEXPNS

☐ Yes

Cellular Therapy Infusion Unit – Manipulation cont.

Activation

☐ No CTIUACTIV

☐ Yes

Induced differentiation

☐ No CTIUINDIFF

☐ Yes

Was the generated cellular product cryopreserved prior to infusion

☐ No CTIUFREEZ

☐ Yes

THERAPY and CELL INFUSION(s)

CHRONOLOGICAL NUMBER OF CELLULAR THERAPY TREATMENT FOR THIS PATIENT ..... CELLTHNR
(please do not include any transplants the patient have had in the past)

This section to be completed only if this is the second or subsequent Cellular Therapy for this patient and the previous Cellular therapy treatment(s) cannot be registered

If number of Advanced Cellular therapy treatment >1:

Same package/product as for the previous advanced cellular therapy treatment? ☐ No ☐ Yes SAMEPACKG

If >1, date of last advanced cellular therapy treatment before this one: ..... - .....-..... DATPREVCINF
yyyy mm dd

If >1, type of last advanced cellular therapy treatment before this one: ☐ Allo ☐ Auto PASTCINFTYP

If >1 and Allograft, Was the same donor used for all prior and current advanced cellular therapy treatments?
☐ No ☐ Yes SAMECIDNR

If >1, was last advanced cellular therapy treatment performed at another institution? DIFFCTINST
☐ No ☐ Yes:

If Yes: CIC if known ..... DIFFCNTR
Name of the institution ..... DINSTNAME
City ..... DCTINSTCTY

⇨ If >1, please submit an Annual follow up form before proceeding, using the latest assessment date before this Cellular Therapy. (This is so we can capture relapse data and other events between advanced cellular therapies).

Additionally, if the patient have had a previoous HSCT please submit Med-AB Follow up form.

Reason for the cellular therapy treatment *(tick all that apply)* REASPRIMCT
*IF INDICATION IS THE TREATMENT OF A **PRIMARY DISEASE***

☐ Treatment of Primary diagnosis
☐ Rescue from disease relapse or progression
☐ Refractory disease
☐ Other, specify .... OTHTREASPC
☐ Prevention of disease relapse or progression
☐ Minimal residual disease reduction

Reason for the cellular therapy treatment *(tick all that apply)*
*IF INDICATION IS THE **TREATMENT OR PREVENTION OF A COMPLICATIONS DERIVED FROM A PREVIOUS TREATMENT***

GvHD
☐ Unrelated to GvHD GVHDRELTRMT
☐ Prevention / prophylaxis of GvHD
☐ Treatment of GvHD

Graft function
☐ Unrelated to graft function GRFNCRELTRMT
☐ Prevention of rejection / promotion of cell engraftment
☐ Graft enhancement
☐ Graft failure treatment

Immune reconstitution
☐ Unrelated to Immune reconstitution IMMRCNSTRT
☐ Immune reconstitution

Patient preparative treatment

Preparative (lymphodepleting) **regimen given?** VCHEMOTH

☐ No (skip to the next page - CELL INFUSION EPISODES)

☐ Yes:

Specification and dose of the preparative regimen
IDAABCCD DOSE DOSEUNIT OTHECHEM

TOTAL PRESCRIBED CUMULATIVE DOSE* as per protocol:
Include any systemic drugs (chemo, growth factors, antibodies, etc.)

Name of drug (any given before day 0)	DOSE	UNITS		
.....		☐ mg/m^2	☐ mg/Kg	☐ AUC**
.....		☐ mg/m^2	☐ mg/Kg	☐ AUC**
.....		☐ mg/m^2	☐ mg/Kg	☐ AUC**
.....		☐ mg/m^2	☐ mg/Kg	☐ AUC**
.....		☐ mg/m^2	☐ mg/Kg	☐ AUC**
.....		☐ mg/m^2	☐ mg/Kg	☐ AUC**
.....		☐ mg/m^2	☐ mg/Kg	☐ AUC**

* Report the total prescribed cumulative dose as per protocol. **Multiply daily dose in mg/kg or mg/m² by the number of days**;
eg. for Busulfan given 4mg/kg daily for 4 days, total dose to report is 16mg/kg

** AUC = Area under the curve

Other type of treatment ☐ No ☐ Yes, specify ....
VOTHERT VOTHERTS

CELL INFUSION EPISODES

Was there more than one cell infusion episode during this treatment or procedure?

☐ No MULTINFEPI

☐ Yes: Number of cell infusion episodes during this procedure ..... NUMINFEPI

Cell infusion episode

If more than one cell infusion episode, replicate this section for each one of them

If more than one Unit was used, indicate the identification of the Cell Infusion Unit given by the Centre as described in the Cell Infusion Unit section

…… NAMCTIPKG2 ***This item is mandatory if more than one unit was used***

Date of cell infusion episode ..... IDAABCCQ

Reconstitution (infusion) procedure CTRECONST

Where was it done? ☐ Bedside ☐ Pharmacy ☐ Cell processing facility

☐ Other, specify…….....

Person in charge of the reconstitution …….. CTRECROLE

Route of infusion *(check all that apply)*

☐ Systemic including Intravenous RTSYSINTR

☐ Other route ..... RTINFOTH RINFOTHSPC

Dose of Cells infused *(complete either the total number of cells or actual volume infused)*

Indicate if only range of doses is available TOTALCELLSNEV

☐ Yes: skip 'Number of cells' question (it means you don't have exact number of cells infused available)

☐ No: Report number of cells infused below

Number of cells…… *(Not adjusted for cell viability)*

Units *(tick one)* ☐ 10^6/kg ☐ 10^6 ☐ 10^8/kg ☐ 10^8 TOTALCELLS TOTALCELLSUNIT

Viability……..% (in percent) VIABILITY

If number of cells infused is not available: Actual volume infused…… ☐ ml VOLINFUSED

Combined /concomitant therapies planned before this Cellular Therapy treatment to optimize efficency CIECONMTRT

☐ No ☐ Yes: specify …… CICNTRTSPC

CIESIMULT Was this treatment given:

☐ Simultaneously to the cellular therapy CIEPCLTHRP

☐ After the cellular therapy episode was finished

Survival Status

VPATSTAT

☐ Alive ☐ Dead

If dead: Main Cause of Death *(check only one main cause)*: VCAUSDTH

- ☐ Relapse or Progression/Persistent disease
- ☐ Secondary malignancy
- ☐ Cellular Therapy related
- ☐ HSCT Related Cause
- ☐ Unknown
- ☐ Other: ..... DEACSBMU

Indicate toxicity related causes of death *(check as many as appropriate)*:

- ☐ GVHD VCSDTGVH
- ☐ Cytokine release syndrome VCSDTCRS
- ☐ Interstitial pneumonitis VCSDTINP
- ☐ Pulmonary toxicity VCSDTPTX
- ☐ Infection: VCSDTINF
  - ☐ bacterial VCSDTBAC
  - ☐ viral VCSDTVIR
  - ☐ fungal VCSDTFUN
  - ☐ parasitic VCSDTPAR
- ☐ Rejection/Poor graft function VCSDTREJ
- ☐ History of severe Veno occlusive disorder (VOD) VCSDTVOD
- ☐ Haemorrhage VCSDTHMR
- ☐ Cardiac toxicity VCSDTCTX
- ☐ Central nervous system (CNS) toxicity VCSDTCNS
- ☐ Gastrointestinal (GI) toxicity VCSDTGIT
- ☐ Skin toxicity VCSDTSKI
- ☐ Renal failure VCSDTREN
- ☐ Multiple organ failure VCSDTMOF

☐ Other:..... DEACSBMR

END OF DAY 0

Advanced Cellular Therapies Form

Status at Last Assessment
(at Day 100, 6 months, Annual Follow Up)

CENTRE IDENTIFICATION

EBMT Code (CIC): .... CENTRNR

Unit: ..... UNIT

Contact person..... MEDNAME

PATIENT DATA

EBMT Unique Identification Code (UIC).....

Hospital Unique Patient Number or Code (UPN): .....UPN
Compulsory, registrations will not be accepted without this item. ***All treatments performed in the same patient must be registered with the same patient identification number or code as this belongs to the patient and not to the treatment.***

Other type of patient identification codes (AIEOP etc.): .....VDOSSIER
(Optional: This item is to be used by the centre to register a patient code for internal use as necessary)

Initials: ....._..... (first name(s) _family name(s)) GIVNAME / FAMNAME

Date of Birth: ..... - ..... - ..... DATPATBD Sex: ☐ Male ☐ Female PATSEX
yyyy *mm* dd *(at birth)*

INDICATE THE ASSESSMENT PERIOD COVERED BY THIS REPORT

☐ **Day 100** ☐ **6 months** ☐ **Annual Follow Up**

RECOVERY

Absolute neutrophil count (ANC) recovery *(Neutrophils ≥0.5X10⁹ /L)* **ENGNEUT**

☐ No: Date of last assessment: ..... - ..... - ..... **DNOENGR**
yyyy mm dd

☐ Yes: Date of ANC recovery: ..... - ..... - ..... *(first of 3 consecutive values after 7 days without transfusion containing neutrophils)* **DATCRGR2**
yyyy mm dd

☐ Never below ☐ Unknown

Platelet reconstitution

Platelets **≥20** x 10^9/l; *(first of 3 consecutive values after 7 days without platelet transfusion)* **VPLAT20A**

☐ No

☐ Yes: Date Platelets ≥ 20 x 10^9/l ..... - ..... - **DPLAT20**
yyyy mm dd

☐ Never below this level
☐ Date unknown: patient discharged before levels reached
☐ Date unknown: out-patient
☐ Unknown

Platelets **≥50** x 10^9/l; *(first of 3 consecutive values after 7 days without platelet transfusion)* **VPLAT50A**

☐ No

☐ Yes: Date Platelets ≥ 50 x 10^9/l ..... - ..... - **DPLAT50**
yyyy mm dd

☐ Never below this level
☐ Date unknown: patient discharged before levels reached
☐ Date unknown: out-patient
☐ Unknown

Date last platelet transfusion:..... - .... - .... ☐ Not applicable: not transfused **DLASTPLT**

RESPONSE AT THE LAST ASSESSMENT

Complete ONLY for DAY 100 and MONTH 6

TO BE ANSWERED ONLY WHEN THE INDICATION WAS THE TREATMENT OF A PRIMARY DISEASE

Best clinical/biological response after the entire Advanced Cellular therapy treatment TUMRSA2

- ☐ Complete remission / Normalisation of organ function / No infection present
- **(AML only)** ☐ CRi (CR with incomplete haematologic recovery)
- ☐ Partial remission / Partial or non normalisation of organ function
- ☐ No response
- ☐ Disease progression or worsening of organ function
- ☐ Not evaluated

Date response evaluated: ..... - ..... - ..... ….. DATRESP
yyyy mm dd

TO BE ANSWERED ONLY WHEN THE INDICATION WAS THE TREATMENT OF COMPLICATIONS DERIVED FROM A PREVIOUS TRANSPLANT/CELLULAR THERAPY

IMMRRESP RESPGRAFT RESPGVHD RESPINFECT

Complication	Response				
GvHD	☐ Resolved	☐ Improved	☐ No response	☐ Progressed	☐ Not evaluated
Graft failure	☐ Resolved	☐ Improved	☐ No response	☐ Progressed	☐ Not evaluated
Immune reconstitution	☐ Resolved	☐ Improved	☐ No response	☐ Progressed	☐ Not evaluated
Infection	☐ Resolved	☐ Improved	☐ No response	☐ Progressed	☐ Not evaluated

Date response evaluated: ..... - ..... - ..... ….. DATERESPCT
yyyy mm dd

LAST CONTACT DATE FOR THIS REPORT

If patient died in the period since the last report, enter the date of death, otherwise enter Date of Advanced Cellular therapy + set period (as indicated above – 100 Days, 6 months, 1 year) approximately.

Last assessment for this report: ..... - ..... - ..... ☐ Not applicable IDAABE
yyyy mm dd

Date of death: ..... - ..... - ..... ☐ Not applicable IDAABE
yyyy mm dd

Current Haematological findings

Hb (g/dL) ..... ☐ Not evaluated HBD

Platelets (10^9/L) ..... ☐ Not evaluated PLATD

Were platelets transfused within 7 days before date of the test? ☐ No ☐ Yes VTRANS2

White Blood Cells (10^9/L) ..... WBCD ☐ Not evaluated

% haematocrit ..... ☐ Not evaluated HAEMATOCRIT

Was RBC transfused within 30 days before date of the test? ☐ No ☐ Yes RBCTRANSF

% Lymphocytes ..... ☐ Not evaluated PLYPBD

% neutrophils ..... PGRPBD ☐ Not evaluated

Was B-Cell Aplasia present since the last assessment? ☐ No ☐ Yes: % (percentage) of B-Cells …… BCELLAPLASFU BCELLPC

Performance score

(COMPLETE ONLY FOR IF PATIENT IS ALIVE)

Performance score of the patient at the last assessment PERFSYST KARNOFSK

SYSTEM USED *(choose only one)*:

☐ Karnofsky or ☐ Lansky: Score: ☐ 20 ☐ 30 ☐ 40 ☐ 50 ☐ 60 ☐ 70 ☐ 80 ☐ 90 ☐ 100

☐ ECOG: ECOG Score: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

Complications since the last report

DO NOT REPORT COMPLICATIONS THAT WERE RESOLVED BEFORE THE ADVANCED CELLULAR THERAPY

DO NOT REPORT COMPLICATIONS THAT WERE PREVIOUSLY REPORTED AS RESOLVED, UNLESS THEY RECURRED

GvHD

Did GvHD occur? ☐ No
(skip to OTHER COMPLICATIONS on page 63)

☐ Yes: GVHDPRES

Type of graft versus host disease (GvHD): GVHDTYP
☐ Acute GvHD
☐ Chronic GvHD

Acute GvHD

Maximum Grade: AGVHGRMX
☐ 0 (none) ☐ I ☐ II ☐ III ☐ IV
☐ Present but grade unknown ☐ Not evaluated

Indicate type: AGVHDTYP
☐ New onset
☐ Recurrent
☐ Persistent

Onset date: ..... - ..... - ..... DATAGVH
yyyy mm dd

Stage:

Skin	☐ 0 (none)	☐ 1	☐ 2	☐ 3	☐ 4	AGVHDSKI
Liver	☐ 0 (none)	☐ 1	☐ 2	☐ 3	☐ 4	AGVHDLIV
Lower GI tract	☐ 0 (none)	☐ 1	☐ 2	☐ 3	☐ 4	AGVHDLGI
Upper GI tract	☐ 0 (none)	☐ 1				AGVHDUGI
Other site affected	☐ No	☐ Yes				AGVHOTHR

Related to Cell Therapy ☐ No ☐ Yes CTHRELATED
Resolved? ☐ No ☐ Yes VGVHDRES

aGvHD treatment

Treatment for aGvHD ☐ No VTRAGVHD
(skip to CHRONIC GVHD section below)

☐ Yes: VTRAGVH2 IDAABCCD ANIMORIG ORIGIN OTHECHEM
☐ Corticosteroids
☐ MoAB: .....
☐ ATG/ALG
☐ Extra-corporeal photopheresis (ECP) TRAGVHECP
☐ Other: specify ..... VAGVHDTO VAGVHDTR

Chronic GvHD CGVHD

Episode: GRAVHOSD
☐ First episode
☐ Recurrence
☐ Continuous since last reported episode
☐ Yes, but resolved
☐ Yes, but resolved and recurred again

DRESCGVH Resolution date: ..... - ..... - .....
yyyy mm dd

Onset date: ..... - ..... - ..... IDAABE
yyyy mm dd

GvHD cont.

Maximum extent during this period

☐ Limited ☐ Extensive ☐ Unknown VCGVHDG

Maximum NIH score during this period

☐ Mild ☐ Moderate ☐ Severe ☐ Not calculated MAXNIHSC

INFECTIOUS COMPLICATIONS WITHIN THIS REPORTING PERIOD

INFECTION RELATED COMPLICATIONS VCOMB100

☐ No -> Skip INFECTIOUS COMPLICATIONS below and go straight to SECONDARY MALIGNANCY on page 60
☐ Yes -> Continue with the INFECTIONS below INFECTIO VOTINCOM INFCPRES IDAABE/BEGINFEP PATHOGEN VOTHPATH TREATEDINF RESOLVEDINF INFSITE OTHSITE

Bacteremia (report all episodes)

☐ No ☐ Yes (report all episodes – copy this page if neccessary):
(In case of the same pathogen, report episodes occuring after 14 days)

1) Onset date: ..... - ..... - ..... (yyyy mm dd) Pathogen: .....
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

2) Onset date: ..... - ..... - ..... (yyyy mm dd) Pathogen: .....
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

3) Onset date: ..... - ..... - ..... (yyyy mm dd) Pathogen: .....
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

4) Onset date: ..... - ..... - ..... (yyyy mm dd) Pathogen: .....
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Invasive fungal disease, including candidemia

☐ No ☐ Yes (report all episodes – copy this page if neccessary):

1) Onset date: ..... - ..... - ..... (yyyy mm dd) Pathogen: ..... Infection site: ☐ Lung ☐ Blood ☐ CNS ☐ Other:.....
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

2) Onset date: ..... - ..... - ..... (yyyy mm dd) Pathogen: ..... Infection site: ☐ Lung ☐ Blood ☐ CNS ☐ Other:.....
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

3) Onset date: ..... - ..... - ..... (yyyy mm dd) Pathogen: ..... Infection site: ☐ Lung ☐ Blood ☐ CNS ☐ Other:.....
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

4) Onset date: ..... - ..... - ..... (yyyy mm dd) Pathogen: ..... Infection site: ☐ Lung ☐ Blood ☐ CNS ☐ Other:.....
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

CNS infection

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Pneumonia

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

C. difficile infection

☐ No ☐ Yes:

Onset date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Abdominal infection

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: …… or specify the type of clinically documented infection, e.g. typhlitis, cholecystits, gastroenteritis, etc:
yyyy mm dd

……

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Hepatitis

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Retinitis

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Cystitis

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Skin infection

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Upper respiratory tract infection

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... (yyyy mm dd) Pathogen: ……..

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

CMV reactivation

(DNA-emia in serum/plasma/blood)

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... (yyyy mm dd) Highest number of copies: ……cp/ml HVALREACTIV

Highest number of copies date: ..... - ..... - ..... (yyyy mm dd) HDATEREACTIV

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

EBV reactivation

(DNA-emia in serum/plasma/blood/PMN)

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... (yyyy mm dd) Highest number of copies: ……cp/ml

Highest number of copies date: ..... - ..... - ..... (yyyy mm dd)

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

HHV6 reactivation

(DNA-emia in serum/plasma)

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... (yyyy mm dd) Highest number of copies: ……cp/ml

Highest number of copies date: ..... - ..... - ..... (yyyy mm dd)

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Adenovirus reactivation

(DNA-emia in serum/plasma)

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... (yyyy mm dd) Highest number of copies: ……cp/ml

Highest number of copies date: ..... - ..... - ..... (yyyy mm dd)

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Other virus reactivation

(DNA-emia in serum/plasma)

☐ No ☐ Yes: specify……

Onset date: ..... - ..... - ..... (yyyy mm dd) Highest number of copies: ……cp/ml

Highest number of copies date: ..... - ..... - ..... (yyyy mm dd)

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Other Infectious Complications

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... (yyyy mm dd) Highest number of copies: ……cp/ml

Highest number of copies date: ..... - ..... - ..... (yyyy mm dd)

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68* Resolved? ☐ No ☐ Yes

Other complications or toxicities during this period VOTCO100

☐ No -> Skip TOXICITIES table below and go straight to INFECTIOUS COMPLICATIONS on page 60
☐ Yes -> Continue with the TOXICITIES below
☐ Unknown

TOXICITIES/(non-infectious) COMPLICATIONS IDAABECA / AUIMPRES / VOTCOMPS / WHOSCORE/ DBEGCOM / TREATED / ONGOING

YOU MUST REPORT AND MARK ALL THE SPECIFIC COMPLICATIONS BELOW EVEN IF THEY ARE ABSENT

Cytokine release syndrome (CRS) (Macrophage Activation Syndrome (MAS))

☐ No ☐ Yes:

Onset date: ..... - ..... - .....
yyyy mm dd

Grade:……

Scale/criteria was used to determine the Grade of CRS…… CRSSCALE

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

Neurotoxicity

☐ No ☐ Yes: Select and complete all that apply

☐ Altered mental status

Onset date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Aphasia

Onset date: ..... - ..... - .....
yyyy mm dd

Grade:……

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Hemiparesis or other focal motor deficit

Onset date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Seizure(s)

Onset date: ..... - ..... - .....
yyyy mm dd

Grade:……

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Tremors

Onset date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Visual hallucinations

Onset date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Encephalopathy

Onset date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Cerebral Oedema

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Other, specify ……

Onset date: ..... - ..... - ..... Grade *(if applicable)*:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

Grade 3 and 4 organ toxicity as per CTCAE

☐ No ☐ Yes: Select and complete all that apply

☐ Skin

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Liver

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Lungs

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Heart

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Kidney

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Gastrointestinal

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

☐ Other organ, specify……..

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

Tumor Lysis Syndrome (TLS)

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Grade:……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

Hemorrhagic stroke

☐ No ☐ Yes:

Onset date: ..... - ..... - .....
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

Bone marrow aplasia

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Specify……
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

Hypogammaglobulinemia

☐ No ☐ Yes:

Onset date: ..... - ..... - .....
yyyy mm dd **HGGLOBIA** **HGGLOBIAW**

Was hypogammaglobulinemia present before the cellular therapy? ☐ No ☐ Yes:

If Yes, was it worsened by the cellular therapy? ☐ No ☐ Yes

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 68*

Resolved? ☐ No ☐ Yes

Insertional mutagenesis

☐ No ☐ Yes:

Onset date: ..... - ..... - .....
yyyy mm dd

Exacerbation of existing neurological disorder

☐ No ☐ Yes:

Onset date: .... - .... - .... Specify……………………………………………
yyyy mm dd

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page* *68*

Resolved? ☐ No ☐ Yes

B-Cell Aplasia (report only If there was no B-Cell Aplasia present at the time of the Cellular Therapy)

☐ No ☐ Yes:

Onset date: .... - .... - ....
yyyy mm dd

Resolved? ☐ No ☐ Yes

Other toxicity/complication

☐ No ☐ Yes:

Onset date: .... - .... - .... Specify……………………………………………
yyyy mm dd

Grade *(if applicable)*:………

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page* *68*

Resolved? ☐ No ☐ Yes

Other toxicity/complication

☐ No ☐ Yes:

Onset date: .... - .... - .... Specify……………………………………………
yyyy mm dd

Grade *(if applicable)*:………

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page* *68*

Resolved? ☐ No ☐ Yes

Other toxicity/complication

☐ No ☐ Yes:

Onset date: .... - .... - .... Specify……………………………………………
yyyy mm dd

Grade *(if applicable)*:………

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page* *68*

Resolved? ☐ No ☐ Yes

Secondary malignancy

Did a secondary malignancy or autoimmune disorder occur?

☐ No ☐ Yes:

SECONDDI
DISMCLFD

Diagnosis: .....

Date of diagnosis: ..... - ..... - .....
IDAABB *yyyy mm dd*

Histologic Type:…….. **VHISTSGD**
(if applicable)

Location:…….. **LOCATION**
(if applicable)

Was sample/biopsy obtained ☐ No ☐ Yes **BIOPSYOBT**
(if applicable)

Is this secondary malignancy derived from cells that composed or were part of the infused medicinal product or advanced cellular therapy product ?

☐ No ☐ Yes ☐ Not applicable ☐ Unknown **RPDRGRAD**

POST-THERAPY TREATMENT

Additional Treatment for Complications and the Main Disease

Please include only systemic treatments

Did the patient undergo additional treatment during or immediately after the cellular therapy or since the last reported assessment? ADDTREAT

Please do not include treatment for aGvHD here, this should be reported in the GvHD section.

☐ No (skip to the last question on this page)
☐ Yes, indicate in tables below

Start date of the additional treatment since last report: .... IDAABC
yyyy mm dd

Unplanned treatment for complications ADDPROT VCHEMOTH IDAABCCD INDICATION

TRETSTAR VINTBTDE
☐ No ☐ Yes, specify in the table below

Drug/Regimen (specify)	Indication (as specified in the Complications section on pages 59 to 60)	Started	Finished
		..........-......... - .... yyyy mm dd	..........-......... - .... yyyy mm dd
		..........-......... - .... yyyy mm dd	..........-......... - .... yyyy mm dd
		..........-......... - .... yyyy mm dd	..........-......... - .... yyyy mm dd
		..........-......... - .... yyyy mm dd	..........-......... - .... yyyy mm dd
		..........-......... - .... yyyy mm dd	..........-......... - .... yyyy mm dd
		..........-......... - .... yyyy mm dd	..........-......... - .... yyyy mm dd

Unplanned treatment for Cellular Therapy failure

☐ No ☐ Yes, specify in the table below ADDPROT VCHEMOTH IDAABCCD INDICATION
TRETSTAR VINTBTDE

Drug/Regimen (specify)	Indication	Started	Finished
		..........-......... - .... yyyy mm dd	..........-......... - .... yyyy mm dd
		..........-......... - .... yyyy mm dd	..........-......... - .... yyyy mm dd
		..........-......... - .... yyyy mm dd	..........-......... - .... yyyy mm dd
		..........-......... - .... yyyy mm dd	..........-......... - .... yyyy mm dd
		..........-......... - .... yyyy mm dd	..........-......... - .... yyyy mm dd
		..........-......... - .... yyyy mm dd	..........-......... - .... yyyy mm dd
		..........-......... - .... yyyy mm dd	..........-......... - .... yyyy mm dd
		..........-......... - .... yyyy mm dd	..........-......... - .... yyyy mm dd

Other type of treatment VOTHERT ☐ No ☐ Yes, specify ………………………………….. VOTHERTS ☐ Unknown

Is patient getting any medications not related to cell therapy or its indications OTHADDTREAT
☐ No ☐ Yes

First Relapse/Progression or Significant worsening after Cellular therapy

TO BE ANSWERED ONLY WHEN THE INDICATION WAS THE TREATMENT OF A PRIMARY DISEASE INCLUDING INFECTIONS

First Relapse or Progression or Significant worsening of organ function of the primary disease
(detected by any method) **VRELPROG**

☐ No

☐ Yes: Date of relapse ..... - ..... - ..... **IDAABE**
yyyy mm dd

☐ Continuous progression since Cellular therapy

Last Disease Status

TO BE ANSWERED ONLY WHEN THE INDICATION WAS THE TREATMENT OF A PRIMARY DISEASE INCLUDING INFECTIONS

Last disease status **VDISESTA**

☐ Complete remission / Normalisation of organ function / No infection present

☐ Partial remission / Partial or non normalisation of organ funcition

☐ No response

☐ Disease progression or worsening of organ function

☐ Not evaluated

(LYMPHOMA only) For **Relapse** status: **HISTPATHOLYM**
Histopathological verification of relapse? ☐ No ☐ Yes

HAEMOGLOBINOPATHY ONLY

Transfusion status **VSVSTAL**

☐ No transfusion required
☐ Transfusions required: Date of the 1st transfusion ..... - ..... - ..... **DATTRANSF**
yyyy mm dd

Hospital admission

Was the patient transferred to the Intensive Care Unit? **INTCARE** ☐ No ☐ Yes

Was inpatient admission and care needed (not ICU)? **INPATIENT** ☐ No ☐ Yes

Quality of Life

Complete ONLY for MONTH 6 and ANNUAL FOLLOW UP

PREGNANCY AFTER CELLULAR THERAPY VCONCEPT

Has patient or partner become pregnant after this Cellular Therapy?

☐ No ☐ Yes: Did the pregnancy result in a live birth? VCONLIVE

☐ No: ABORTBIRTH
- ☐ Abortion (elective, therapeutic, spontaneous)
- ☐ Stillbirth

☐ Yes: LIVEBIRTH LTERMBIRTH

New Born Status:
- ☐ Healthy
- ☐ Affected by a disease
- ☐ **Information not provided**

Length of term:
- ☐ Full-term
- ☐ Premature
- ☐ **Information not provided**

☐ Unknown

☐ Unknown

Survival Status

VPATSTAT

☐ Alive ☐ Dead ☐ Check here if patient lost to follow up

If dead: Main Cause of Death *(check only one main cause)*: VCAUSDTH
- ☐ Relapse or Progression/Persistent disease
- ☐ Secondary malignancy
- ☐ Cellular Therapy related
- ☐ HSCT Related Cause
- ☐ Unknown
- ☐ Other: ..... DEACSBMU

Indicate toxicity related causes of death *(check as many as appropriate)*:
- ☐ GVHD VCSDTGVH
- ☐ Cytokine release syndrome VCSDTCRS
- ☐ Interstitial pneumonitis VCSDTINP
- ☐ Pulmonary toxicity VCSDTPTX
- ☐ Infection: VCSDTINF
  - ☐ bacterial VCSDTBAC
  - ☐ viral VCSDTVIR
  - ☐ fungal VCSDTFUN
  - ☐ parasitic VCSDTPAR
- ☐ Rejection/Poor graft function VCSDTREJ
- ☐ History of severe Veno occlusive disorder (VOD) VCSDTVOD
- ☐ Haemorrhage VCSDTHMR
- ☐ Cardiac toxicity VCSDTCTX
- ☐ Central nervous system (CNS) toxicity VCSDTCNS
- ☐ Gastrointestinal (GI) toxicity VCSDTGIT
- ☐ Skin toxicity VCSDTSKI
- ☐ Renal failure VCSDTREN
- ☐ Multiple organ failure VCSDTMOF

☐ Other:..... DEACSBMR

Persistence of the Infused Cells

Were tests performed to detect the persistence of the cellular products during this period?
PRSTSTDONE

☐ No ☐ Yes: Date of the last test ..... - ..... - ..... PRSTSTDATE
yyyy *mm* *dd*

CELPRDSOUR CELPRDSOSPC
Source of cells used for the test: ☐ Bone Marrow ☐ Peripheral Blood ☐ Tumour ☐Other, specify……..

Technique used MOLPCR FLWCYTOMTR CHIMAETECH IMAGETECH IMHISTECH OTHTSTTECH / OTHTECHSPC

☐ Molecular (PCR) ☐ Flow cytometry ☐ Chimaerism ☐ Imaging ☐ Immunohistochemistry

☐ Other, specify ……..……..

Were cells detected? CELPRDTDET

☐ No

☐ Yes

END OF FOLLOW UP

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-X19 in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-3)
Protocol Number:	KTE-C19-103 (ZUMA-3)
Kite Investigational Product:	KTE-X19
USAN:	Brexucabtagene Autoleucel
IND Number:	016675
EudraCT Number:	2015-005009-35
ClinicalTrials.gov Identifier:	NCT02614066
Clinical Study Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Key Sponsor Contacts:	The medical monitor name and contact information is included on the Study Contact Lists distributed by the CRO.
Protocol Version/Date:	Original: 07 May 2015 Amendment 7: 14 December 2021

SPONSOR AND INVESTIGATOR SIGNATURE PAGE

KITE PHARMA, INC.
2400 BROADWAY
SANTA MONICA, CA 90404

STUDY ACKNOWLEDGEMENT

A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-X19 in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-3)

Amendment 7.0, 14 December 2021

This protocol has been approved by Kite Pharma, Inc. The following signature documents this approval.

Dr. Behzad Kharabi

Kite Medical Monitor Name (Printed)

DocuSigned by:
4C6489CED31042F...

Signature

January 5, 2022 | 3:36:11 AM PST

Date

INVESTIGATOR STATEMENT

I have read the attached protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete this study within the time designated.

I agree to comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations and guidelines. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Kite Pharma, Inc. I will discuss this material with them to ensure that they are fully informed about the investigational product and study.

I agree and will ensure that financial disclosure statements will be completed by:

- Me (including, if applicable, my spouse, legal partner and dependent children)
- Sub-Investigators (including, if applicable their spouse, legal partner and dependent children) at the start of the study and for up to 1 year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the clinical investigation without prior written consent from Kite Pharma Inc.

Principal Investigator Name (Printed)

Signature

Date

Site Number

STUDY GLOSSARY

AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CAR	chimeric antigen receptor
CAR+	chimeric antigen receptor positive
CBC	complete blood count
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CPF	cell processing facility
CR	complete remission
CRh	complete remission response with partial hematologic recovery
CRi	complete remission response with incomplete hematologic recovery
CRF	case report form
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CTCAE	common terminology criteria for adverse events
ddPCR	droplet digital polymerase chain reaction
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of remission
DSMB	data safety monitoring board
DVT	deep vein thrombosis
eACT™	engineered autologous cell therapy
ECHO	echocardiogram
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEG	electroencephalogram
End of Study for individual subject	Defined as when the last day that protocol specified assessments are conducted for an individual subject
End of Study (primary completion)	Defined as when the last subject is assessed or received an intervention for the purposes of final collection of data for the primary endpoint at Week 8
End of Study (end of trial)	Defined as when the last subject is assessed or received an intervention for evaluation in the study, including survival assessments
High Burden Disease	M3 marrow (>25% leukemic blasts) or ≥ 1000 blasts/mm^3 in the peripheral circulation
HLH	Hemophagocytic lymphohistiocytosis
ICF	informed consent form
IHC	immunohistochemistry

IL	interleukin
IL-2R	interleukin-2 receptor
IP	investigational product
IPM	Investigational product manual
IRB/IEC	institutional review board/independent ethics committee
KTE-X19	autologous T cells transduced with retroviral vector containing anti-CD19 CD28/CD3-zeta chimeric antigen receptor
LMWH	low-molecular weight heparin
LTFU	long term follow-up
LVEF	left ventricular ejection fraction
mITT	modified intend to treat
MTD	maximum tolerated dose
MRD	minimal residual disease
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
OS	overall survival
PBMC	peripheral blood mononuclear cells
PET	positron emission tomography
Ph^+	Philadelphia chromosome positive
PMBCL	primary mediastinal B-cell lymphoma
PD	progressive disease
PR	partial response
qPCR	quantitative polymerase chain reaction
RCR	replication competent retrovirus
RFS	relapse-free survival
r/r	relapsed/refractory
SAE	serious adverse event
scFv	single chain variable fragment
SMZL	splenic marginal zone lymphoma
SOA	schedule of assessments
SOC	standard of care
SCT	stem cell transplant
Study day 0	Defined as the first day that KTE-X19 is administered to the subject
TEAEs	treatment-emergent adverse events
TKI	tyrosine kinase inhibitor
TLS	tumor lysis syndrome
TNF	tumor necrosis factor
ULN	upper limit normal
WBC	white blood cell

PROTOCOL SYNOPSIS

Title:	A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-X19 in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-3)
Indication:	The indication is for the treatment of adult subjects with B-precursor r/r ALL**.**
Study Design:	ZUMA-3 is a Phase 1/2, multicenter, open-label study evaluating the safety and efficacy of KTE-X19 in adult subjects with relapsed or refractory B-precursor ALL. In this study, relapsed or refractory is defined as one of the following: primary refractory; first relapse following a remission lasting ≤ 12 months; relapsed or refractory after second-line or higher therapy; relapsed or refractory after allogenic SCT (provided the transplant occurred ≥ 100 days prior to enrollment and that no immunosuppressive medications were taken ≤ 4 weeks prior to enrollment). **Phase 1 Study** During Phase 1, approximately 3-12 subjects with high burden [M3 marrow (>25% leukemic blasts) or ≥1000 blasts/mm^3 in the peripheral circulation] r/r ALL disease who are evaluable for DLT will be assessed to evaluate the safety of KTE-X19. A safety review team (SRT) that is internal to the study sponsor, and in collaboration with at least 1 study investigator, will review safety data and make recommendations regarding further enrollment in Phase 1 or proceeding to Phase 2 based on the incidence of DLTs and overall safety profile of KTE-X19. Up to approximately 40 additional subjects with high or low burden disease may be enrolled to further assess safety (see Figure 1, Section 3.1 and Section 9.6). **Phase 2 Study** During Phase 2, approximately 50 subjects in the modified-intention to treat (mITT) set will be assessed to evaluate the efficacy and safety of KTE-X19. An independent Data Safety Monitoring Board (DSMB) will review safety data through one interim analysis during the Phase 2 portion of the study. In this interim analysis, the DSMB will review safety data after 20 Phase 2 subjects have been treated with KTE-X19 and had the opportunity to be followed for 30 days after the KTE-X19 infusion. Each subject will provide consent and be evaluated for study participation. Once deemed eligible and enrolled into the study, each subject will follow the same study treatment schedule and procedural requirements, independent of the phase of the study, and proceed through the following study periods:

	• Screening period • Enrollment/Leukapheresis period • Bridging chemotherapy and cerebrospinal fluid (CSF) prophylaxis period • Conditioning chemotherapy period • Investigational Product (IP) treatment period • Post treatment assessment period • Long term follow-up period For study requirements assigned to each study period, refer to the schedule of assessments and Section 7 for details.
Study Objectives:	**Phase 1 Study** The primary objective of Phase 1 is to evaluate the safety of KTE-X19. **Phase 2 Study** The primary objective of Phase 2 is to evaluate the efficacy of KTE-X19, as measured by the overall complete remission rate defined as complete remission (CR) and complete remission with incomplete hematologic recovery (CRi) in adult subjects with r/r ALL (Appendix 1). Secondary objectives will include assessing the safety and tolerability of KTE-X19 and additional efficacy endpoints.
Hypothesis:	This study is designed to differentiate between a treatment that has a true overall complete remission rate of 40% or less and a treatment with a true overall complete remission rate of 65% or more. The hypothesis is that the overall complete remission rate to KTE-X19 is significantly greater than 40%.
Primary Endpoints:	• Phase 1: Incidence of adverse events (AEs) defined as dose-limiting toxicities (DLTs) in the DLT evaluable set • Phase 2: Overall complete remission rate (CR + CRi) per independent review (Appendix 1)
Secondary Endpoints:	• Overall complete remission rate (CR + CRi) per investigator assessment (Appendix 1) • Duration of Remission (DOR) • Minimal Residual Disease (MRD) negative rate • Allogeneic stem cell transplant (Allogeneic SCT) rate • Overall survival (OS) • Relapse-free Survival (RFS)

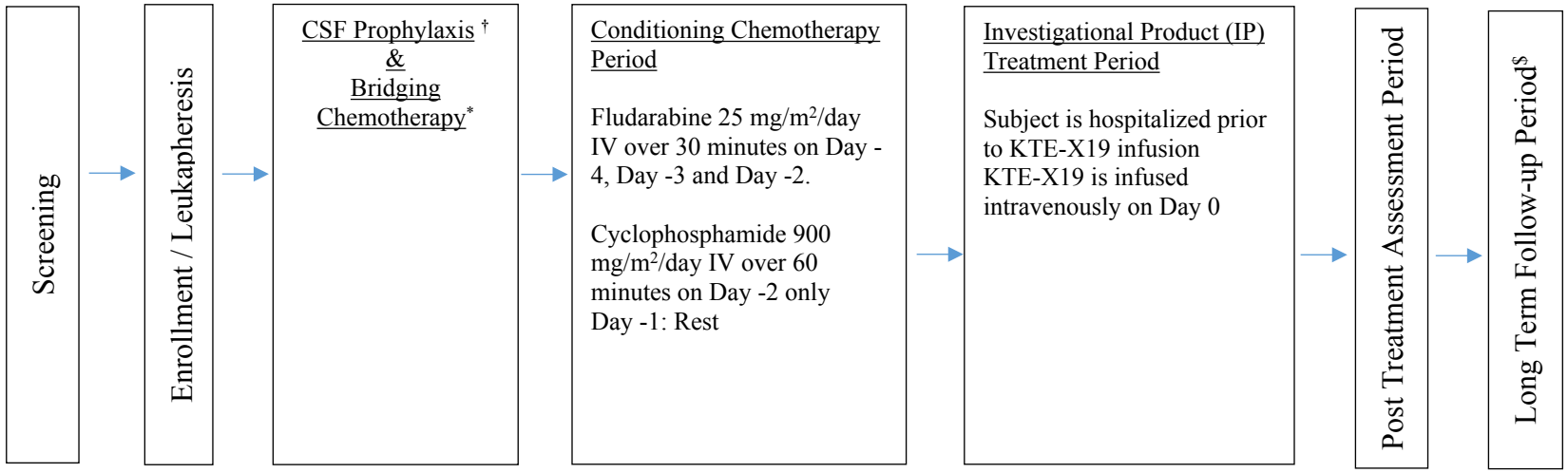
	• Incidence of AEs and common terminology criteria for adverse events (CTCAE) grade changes in safety laboratory values • Incidence of anti-KTE-X19 antibodies • Changes over time in the EQ-5D score and VAS score (phase 2 only) **Exploratory Endpoints** • Treatment-related mortality rate100 days post-allogeneic SCT • Complete remission with partial hematological recovery (CRh) • Blast-free hypoplastic or aplastic bone marrow rate • Partial remission (PR) rate • The overall complete remission rate (CR +CRi), MRD-negative rate, and DOR among subjects retreated with KTE-X19 post-progression • Level and activity of CAR+ T cells, as well as presence of CD19+ cells in blood and bone marrow • Levels of cytokines in serum and CSF
Sample Size	In total, up to approximately 100 subjects may be enrolled and treated with KTE-X19 in the study in Phase 1 and 2 combined (see Sections 9.6 and 10.3). • Phase 1: Approximately 3-12 subjects evaluable for DLT and up to approximately 40 additional subjects • Phase 2: Approximately 50 subjects in the mITT set
Study Eligibility	Please refer to Section 5 for a complete and detailed list of inclusion and exclusion criteria for both phases of the study.
Treatment	Bridging chemotherapy: • Bridging chemotherapy is recommended for all subjects particularly for those subjects with high disease burden at screening [M3 marrow (>25% leukemic blasts) or ≥1000 blasts/mm^3 in the peripheral circulation] • If prescribed, bridging chemotherapy must be administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy. • Allowed bridging chemotherapy regimens are listed in Section 6.3, Table 2. Doses listed are recommended and can be adjusted for age/comorbidities or per local or institutional guidelines. • Refer to Sections 6.3 and 7.11.4 for further details.

	CSF Prophylaxis: • All subjects will receive CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines (eg, methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, or dexamethasone 4 mg or equivalent steroid dose). • CSF prophylaxis will be administered any time during screening (eg, at time of screening lumbar puncture) through 7 days prior to KTE-X19 infusion. • Subjects who are enrolled with CNS-2 disease at baseline must receive CSF prophylaxis after leukapheresis and at least 7 days prior to KTE-X19 infusion, unless otherwise approved by the Kite Medical Monitor. • Multiple doses of CSF prophylaxis can be given per investigator discretion in accordance with institutional guidelines, but at least 7 days must pass between the last dose of CSF prophylaxis and KTE-X19 infusion. • Additional CSF prophylaxis may be given post-KTE-X19 infusion per investigator discretion in accordance with institutional guidelines, but should be avoided for at least 8 weeks after KTE-X19 infusion if possible. • Refer to Sections 6.4 and 7.11.5 for further details. Conditioning Chemotherapy: • All subjects will receive conditioning chemotherapy consisting of fludarabine and cyclophosphamide. • Fludarabine will be given at a dose of 25 mg/m^2/day intravenously (IV) over 30 minutes on Day-4, Day -3, and Day 2 prior to KTE-X19 infusion. • Cyclophosphamide will be given at a dose of 900 mg/m^2/day IV over 60 minutes on Day -2 prior to KTE-X19 infusion. • Refer to Sections 6.5 and 7.11.6 for further details. Investigational Product: • The day of KTE-X19 infusion is considered Day 0. • KTE-X19 infusion will be administered at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg, 1 x 10^6 anti-CD19 CAR T cells/kg, or 0.5 x 10^6 anti-CD19 CAR T cells/kg (see Figure 1, Section 3.1 and Section 9.6). • All subjects will be hospitalized to receive KTE-X19 infusion followed by a minimum 7 day observation period unless otherwise required by country regulatory agencies (refer to Appendix 3 for details). • Refer to Sections 6.6 and 7.11.7 for further details.

Procedures	At specific time points as outlined in the schedule of assessments, subjects will undergo the following procedures: • Collection of informed consent, general medical history including previous treatments for ALL, physical exam including height and weight, vital signs, ECOG performance status, and neurological assessments. • Lumbar punctures for collection of cerebral spinal fluid (CSF). • Bone marrow biopsies/aspirates. • If applicable, imaging modality appropriate for the anatomical site and clinical scenario (eg, positron emission tomography [PET], magnetic resonance imaging [MRI] for central nervous system [CNS] lesion, ultrasound for testicular lesion, computed tomography [CT] for intra-abdominal or thoracic lesions), will be performed to assess extramedullary disease status. • Blood will be drawn and assessed locally for complete blood count (CBC) with differential, chemistry panels, C-reactive protein, and CD3 count. CD19 expression will be assessed locally in subjects with prior blinatumomab treatment by flow cytometry or immunohistochemistry (IHC) on blasts obtained from peripheral blood or bone marrow. • Women of child-bearing potential will undergo a urine or serum pregnancy test. • Blood will be drawn and submitted to the central lab for: cytokines, lymphocyte subsets, anti-KTE-X19 antibodies, replication competent retrovirus (RCR) and anti-CD19 CAR T cell analysis. • Subjects will also undergo a baseline electrocardiogram (ECG) and echocardiogram (ECHO) • Leukapheresis. • Routinely throughout the conduct of the study, subjects will be asked to report concomitant medications and adverse events. • Subjects in phase 2 will complete the EQ-5D questionnaire.
Safety Review Team and Data Safety Monitoring Board	During Phase 1, approximately 3-12 subjects with high burden [M3 marrow (>25% leukemic blasts) or ≥1000 blasts/mm^3 in the peripheral circulation] r/r ALL disease who are evaluable for DLT will be assessed to evaluate the safety of KTE-X19. A safety review team (SRT) that is internal to the study sponsor, and in collaboration with at least 1 study investigator, will review safety data and make recommendations regarding further enrollment in Phase 1 or proceeding to Phase 2 based on the incidence of DLTs and overall

	safety profile of KTE-X19. Up to approximately 40 additional subjects with high or low burden disease may be enrolled to further assess safety (see Figure 1, Section 3.1 and Section 9.6). During Phase 2, approximately 50 subjects in the modified-intention to treat (mITT) set will be assessed to evaluate the efficacy and safety of KTE-X19. An independent Data Safety Monitoring Board (DSMB) will review safety data through one interim analysis during the Phase 2 portion of the study. In this interim analysis, the DSMB will review safety data after 20 Phase 2 subjects have been treated with KTE-X19 and had the opportunity to be followed for 30 days after the KTE-X19 infusion.
Statistical Considerations	The primary endpoint for the Phase 2 study is the overall complete remission rate (CR and CRi) per independent review (Appendix 1). This endpoint will be based on a mITT population consisting of all Phase 2 subjects who receive KTE-X19 dose (see Section 10.5). This study uses a single-arm design to test for an improvement in overall complete remission rate. For the test of efficacy this study has approximately 93% power to distinguish between an active therapy with a 65% true overall complete remission rate from a therapy with an overall complete remission rate of 40% or less with a 1-sided alpha level of 0.025. During Phase 1, the SRT will review safety data after 3 subjects in the DLT evaluable set (see Section 10.5) have had the opportunity to be followed for 28 days after the KTE-X19 infusion (see Section 9.6). During Phase 2, one interim and one primary analysis will be performed. The interim analysis is for safety only and will be performed by the DSMB after 20 Phase 2 subjects have been treated with KTE-X19 and had the opportunity to be followed for 30 days after the KTE-X19 infusion. Additional interim analyses for safety may be requested by the DSMB. The primary analysis will occur when the overall study enrollment is complete and the last treated subject in the mITT set has had the opportunity to complete the month 6 disease assessment. A secondary endpoint, MRD-negative rate, will be tested against an MRD-negative rate of 30% if the testing of the primary endpoint is significant.

Study Schema



† CSF Prophylaxis (administered any time during screening through 7 days prior to KTE-X19 infusion):
All subjects will receive CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines must be administered. CSF prophylaxis may be administered with the screening lumbar puncture. See Section 6.4 for additional details.

* Bridging Chemotherapy (administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy)
Bridging chemotherapy is recommended for all subjects particularly those subjects with high disease burden at screening [M3 marrow (>25% leukemic blasts) or ≥1000 blasts/mm^3 in the peripheral circulation]. See Section 6.3 for details.

$ After completion of the Month 24 visit, subjects who received an infusion of KTE-X19 will complete the remainder of the 15-year follow-up assessments in a separate long-term follow-up study, KT-US-982-5968.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

1. OBJECTIVES

The primary objective of Phase 1 is to evaluate the safety of KTE-X19.

The primary objective of Phase 2 is to evaluate the efficacy of KTE-X19, as measured by the overall complete remission rate defined as complete remission (CR) and complete remission with incomplete hematologic recovery (CRi) in adult subjects with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL). Secondary objectives will include assessing the safety and tolerability of KTE-X19, additional efficacy endpoints, and change in EQ-5D scores.

2. DISEASE BACKGROUND AND RATIONALE

2.1. Overview of ALL and Epidemiology

Acute lymphoblastic leukemia is a heterogeneous group of lymphoid disorders that results from the clonal proliferation of immature lymphocytes of B-cell or T-cell lineage in the blood, bone marrow, and other organs. The disease occurs with a bimodal age distribution, with 60% of cases diagnosed in patients less than 20 years old, and 25% of cases diagnosed at age 45 years or greater. In the United States there are approximately 6,000 new ALL cases diagnosed per year, of which 2,500 are in adults. While 5-year survival rates are 80-90% in children, less than 25% of adults achieve long-term survival, and the majority of the 1,400 ALL deaths per year in the United States are in adults {National Comprehensive Cancer Network 2014, Siegel 2014}. While initial CR rates in adults are high (80-90%) and the median duration of first remission in most studies is 18 months or longer, most patients eventually experience relapse {Kantarjian 2004, Kantarjian 1994, Larson 1995, Rowe 2005}. Outcomes in the second-line and beyond setting with chemotherapy are poor with CR rates of approximately 20-40%, being lower in patients with relapse within 12 months of initial response, and overall survival (OS) being approximately 6 months, making the relapsed/refractory setting the area of greatest unmet need in ALL {Faderl 2011, Fielding 2007, Kantarjian 2003, O'Brien 2013, Tavernier 2007, Thomas 1999}.

2.2. Diagnosis and Subtyping of ALL

Diagnosis of ALL requires at least 20% lymphoblasts in the bone marrow {Harris 1999}. ALL is then further classified into 1 of 3 major subtypes by immunophenotyping: B-precursor ALL (70%), mature B-cell ALL (Burkitt lymphoma; 5%), and T-cell ALL (25%). B-cell ALLs are generally $CD10^+$, $CD19^+$, and $CD79a^+$, although precursor B-cell ALLs may be $CD10^-$. Mature B-cell ALLs additionally express surface immunoglobulin (Ig). T-cell ALLs express T-cell markers such as CD3, CD4, and CD8. The 3 immunophenotypic subtypes are associated with non-overlapping prognoses and treatments making the classification clinically relevant {National Comprehensive Cancer Network 2014}. B-precursor ALL comprises the majority of all adult ALL cases.

2.3. Philadelphia Positive vs. Negative ALL

Approximately 20-30% of adults and a small percentage of children with ALL are Philadelphia chromosome positive (Ph^+), and the majority of Ph^+ cases are of B-cell lineage {Lee 2011}. Ph^+ status confers poor prognosis, with a 5-year event-free survival (EFS) rate of 36% vs 16% and an OS rate of 41% vs. 22% in Philadelphia chromosome negative (Ph-) vs. Ph+ patients {Moorman 2007}. Ph+ status also allows for additional treatment with Abl tyrosine kinase inhibitors (TKIs) such as imatinib or dasatinib.

2.4. Treatment and Prognosis

Several anti-neoplastic agents are given in varying doses and schedules based on regional preferences and patient tolerability in 3 distinct phases for 1st line treatment: induction, intensified consolidation, and maintenance. Central nervous system (CNS) prophylaxis

accompanies induction and consolidation. The goals of treatment are to reconstitute normal hematopoiesis, prevent emergence of resistant subclones, eliminate minimal residual disease, and provide prophylaxis to sanctuary sites. Stem cell transplant also plays a role in the management of ALL, and tyrosine kinase inhibitors are added to chemotherapy and transplant regimens in patients with Ph^+ disease.

2.4.1. First-line Treatment

Most first-line regimens are a variation of either the Berlin-Frankfurt-Münster/Children's Oncology Group (BFM/COG) 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 TKI such as imatinib is included in the treatment regimen for patients with Ph^+ disease. Dexamethasone appears to decrease the risk of CNS relapse and improve EFS compared to prednisone, but at the risk of increased toxicity and no OS advantage {Mitchell 2005, Pui 2006}. The hyper-CVAD regimen which has demonstrated efficacy in ALL is a variation on the CALGB regimen with alternating regimens of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone with high-dose methotrexate and cytarabine {Kantarjian 2004}. First-line regimens yield CR rates of 80-90% in adults. Despite the high CR rates and a median duration of first remission of at least 18 months, most patients eventually relapse.

2.4.2. Second-line and Beyond Treatment

The salvage setting represents the area of greatest need in adult ALL given the poor outcomes achieved with chemotherapy in adults who have relapsed or refractory ALL. Second-line chemotherapy yields remissions in about 20-40% of patients, with the remission rate being lower in patients who relapse within 12 months of an initial response (Table 1).

In the third line and beyond setting, complete remissions with chemotherapy are seen in at most 20% of patients, and the majority of remissions are short lived {Faderl 2011, Fielding 2007, Kantarjian 2003, O'Brien 2013, Tavernier 2007, Thomas 1999}. Although long-term disease free survival (DFS) rates of autologous stem cell transplantation (ASCT) are superior to chemotherapy in the salvage setting (approximately 40% vs 20%), only 30-40% of patients who achieve a second CR are eligible for SCT, and fewer than half of the patients who achieve a second CR have enough time prior to relapse to make it to transplant {Herzig 1987, Kolb 2009, Terwey 2009}, with rates as low as 5% in adults being reported in some series {Thomas 1999}.

In December 2014, the bispecific CD19-directed CD3 T-cell engaging agent blinatumomab was granted accelerated approval in the US for the treatment of Ph^- relapsed or refractory B-cell precursor ALL {BLINCYTO 2017}. The approval was granted based primarily on findings from a single-arm study of 185 evaluable patients with r/r B-precursor ALL (relapsed with first remission duration of ≤12 months in first salvage or relapsed or refractory after first salvage therapy or relapsed within 12 months of SCT). CR was achieved in 32% of patients, and an additional 9% had CRh. The majority of responses (81%) occurred within cycle 1 of treatment, 75% of those with CR/CRh had an minimum residual disease (MRD)-negative response, and the SCT rate among those who achieved CR/CRh was 39%. Duration of response/relapse-free survival in patients who had CR/CRh was 5.9 months. Results from a second study of blinatumomab, a Phase 3 trial which randomized adults with r/r ALL 2:1 to blinatumomab

versus 1 of 4 standard of care (SOC) chemotherapy regiments, have also recently been reported. A total of 405 patients were randomized, and a prespecified interim analysis occurred after 248 deaths. Median OS was 7.8 months (95% CI: 5.7, 10.0) for blinatumomab and 4.0 months (95% CI: 2.9, 5.4) for SOC (p=.011; hazard ratio=0.71), surpassing the prespecified boundary p value of 0.0183. Based on these results, this study was terminated early upon the recommendation of the study's Data Safety Monitoring Board {Topp 2016}. No studies have yet reported the outcomes of patients in the post-blinatumomab setting.

Table 1 below summarizes representative data in the salvage setting for adult ALL. Given the promising early data for chimeric antigen receptor (CAR) T-cell therapy in r/r ALL (see Section 2.6), this trial evaluates KTE-X19 in this difficult setting.

Table 1. Complete Response (CR) Rate in Adult B-Precursor Acute Lymphoblastic Leukemia (B-ALL) in the Relapsed/Refractory Setting

Trial/Reference	Treatment	Criteria	N	CR rate
Second line chemotherapy (relapsed or refractory after initial therapy for de novo disease)				
Thomas Cancer 1999	Various chemotherapy or SCT regimens	Primary refractory (24%) or primary relapsed (76%) disease	314	31% overall • 22% for patients with 1st CR of duration 1-11.9 months (n=146) • 41% for patients with first CR of duration >12 months (n=93) • 20% for Ph^+ (n=55) • 34% for primary refractory (n=75)
Tavernier Leukemia 2007	Various systemic or SCT regimens	Relapsed or refractory after initial therapy, Ph^- Relapsed or refractory after initial therapy, Ph^+	340 81	46% 37%
Welborn Am J Hema 1994	Various chemotherapy regimens	Relapsed or refractory ALL (primarily second line patients)	609	34%
Faderl Clin Lymphoma Myeloma Leuk 2011	hCVAD	Refractory (11%) or relapsed (89%; 76% of all patients in 1st relapse)	90	46% (median CR1 of responders = 16 months)
Third line or beyond chemotherapy				
Kantarjian Blood 2003	Clofarabine	2nd or subsequent salvage	8	13%
Advani Br J Haematol 2010	Clofarabine+ cytarabine	Patients in ≥ 2nd relapse	16	19% (CR/CRi)[A]
O'Brien JCO 2013	Liposomal vincristine sulfate	Ph^- ALL in 2nd or greater relapse	65	20% (CR/CRi)[A]
Novel targeted agents				
Blinatumomab USPI	Blinatumomab	Relapsed/refractory B-precursor ALL	185	• 32% CR • 9% CRh[B]
Kantarjian NEJM 2016	Anti-CD22-calecheamicin (inotuzumab oogamicin)	Relapsed and refractory ALL	49 (46 adults)	• 36% CR • 45%CRi[A] • OS HR 0.77 (97.5% CI, 0.58-1.03) inotuzumab vs. chemotherapy

A Complete remission with incomplete hematologic recovery (CRi)
B Complete remission with partial hematologic recovery (CRh)
C Complete marrow response (CMR)

2.4.3. Minimal Residual Disease (MRD)

Several studies have shown that the achievement of a minimum residual disease (MRD)-negative response (<0.01% lymphoblasts in the bone marrow) with ALL treatment is associated with prolonged leukemia remission in both pediatric and adult ALL patients {Campana 2010, Cazzaniga 2011}. However, not all subjects who achieve a morphological complete remission achieve a MRD-negative remission. In a large study by the Children's Oncology Group randomizing patients to different induction and maintenance regimens, 1788 of 2422 (74%) of subjects who had a remission (<10% bone marrow blasts) achieved MRD-negative status {Borowitz 2015}. Treatment with the bispecific T cell engager blinatumomab produces a similar proportion of MRD-negative responses, 8 of 14 (53%) pediatric patients with a CR had an MRD-negative response {von Stackelberg 2016}. Minimum residual disease-negative rates are similar in adults. With blinatumomab, 60 of 73 (82%) adult patients who achieved a CR or CRh had an MRD-negative response.

2.5. Study Rationale

Most advanced cancers eventually become refractory to conventional therapies and new treatment modalities are needed. Immunotherapy, which is based on the enhancement of an immune response against the tumor, is a promising approach to treating many cancer types. T cells play an important role in destroying diseased cells throughout the body. Studies with immune checkpoint inhibitors and tumor infiltrating lymphocytes have demonstrated the potential of T cells to treat cancer. T cells need to possess the appropriate specificity for a tumor, be present in sufficient numbers, and overcome any local immunosuppressive factors to be effective. Engineered T cells are a promising approach for cancer therapy {Kershaw 2013}.

Engineered Autologous Cell Therapy (eACT™) is a process by which a patient's own T cells are collected and subsequently genetically altered to recognize and target antigens expressed on the cell surface of specific malignancies {Kochenderfer 2013}. The ability to genetically engineer human T cells and use them to mediate cancer regression in patients has been demonstrated in a number of studies {Davila 2014, Lee 2015, Maude 2014} and has opened possibilities for the treatment of patients with a wide variety of cancer types including B-cell malignancies expressing the CD19 antigen.

Given the poor outcomes which have been achieved to date in adults with r/r ALL (Table 1), this trial will enroll adult subjects with r/r B-precursor ALL as evidenced by failure to achieve or maintain a response to prior systemic therapy, or by recurrence after allogeneic SCT. Patients with T-cell lineage ALL will not be enrolled since their malignancies are $CD19^-$ and will likely not respond to a CD19 directed agent.

2.5.1. CD19 and Expression

CD19 is a 95 kD transmembrane protein expressed only in the B-cell lineage. It is expressed in all normal B cells starting at the pre-B cell stage until the final differentiation stage and is not expressed in pluripotent hematopoietic stem cells or most plasma cells. The pattern of CD19 expression is maintained in B-cell malignancies including all subtypes of B-cell non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and non T-cell acute lymphoblastic leukemia (ALL) {Blanc 2011} with the exception of multiple myeloma.

2.5.2. Anti-CD19 CAR T-cell Product

Anti-CD19 CAR T cells are autologous human T cells that have been engineered to express an extracellular single chain variable fragment (scFv) with specificity for CD19 linked to an intracellular signaling part comprised of signaling domains from CD28 and CD3ζ molecules arranged in tandem. KTE-X19 is an anti-CD19 CAR T cell product being developed by Kite Pharma under ZUMA-3.

Two different manufacturing processes are used for Kite's anti-CD19 CAR T cell products: CLP and XLP. These 2 processes yield different products per FDA and EMA. The processes differ in lymphocyte enrichment and activation steps to address the needs of making products from patients with different tumor indications. KTE-X19 is manufactured via the XLP manufacturing process for subjects that are characterized by having high numbers of CD19-expressing circulating tumor cells (B-cell acute lymphoblastic leukemia, CLL, and MCL). All clinical subject lots manufactured for ZUMA-3 use the XLP process. The introduction of the KTE-X19 code is an administrative name change and does not change the manufactured product.

Briefly, from the leukapheresis product the T cells in the harvested leukocytes are enriched by binding to magnetic beads coated with anti-CD4 and anti-CD8 antibodies. T-cells are activated by culturing with anti-CD3 and anti-CD28 antibodies, and are then transduced with a retroviral vector containing an anti-CD19 CAR gene. These engineered T cells are then propagated in culture to generate a sufficient number of cells for administration.

The CAR vector construct utilized in KTE-X19 is identical to the one used in National Cancer Institute (NCI) protocols (Surgery Branch protocol 09-C-0082; IND 13871; Pediatric Branch (Protocol 12-C-0112G; IND: 14985). Refer to the current KTE-X19 IB for additional description of the T-cell product.

2.6. Clinical Experience with Anti-CD19 CAR T Cells in Studies Conducted at the National Cancer Institute (NCI)

The same CAR construct used in KTE-X19-103 was previously evaluated at the NCI in children and young adults with r/r ALL {Lee 2015}; (clinicaltrials.gov number NCT01593696), and in adults with r/r B-cell malignancies {Kochenderfer 2015}; (clinicaltrials.gov number NCT00924326).

Refer to the current KTE-X19 IB and publications cited for details on the study design and the safety and efficacy outcomes observed in these studies.

2.7. KTE-C19-101 ZUMA-1 Experience

ZUMA-1 is a Phase 1-2 multicenter, open-label study evaluating the safety and efficacy of KTE-C19 in adult subjects with refractory DLBCL, PMBCL, and transformed follicular lymphoma (TFL). The primary analysis for the study, which has been completed, was based on analysis of the data from 92 subjects in the phase 2 portion of the study who had the opportunity to be followed for at least 6 months after infusion of KTE-C19. The study met its primary endpoint: the objective response rate per International Working Group 2007 criteria {Cheson 2007} in these 92 subjects was 82% (95% CI: 72%, 89%), which was significantly higher than the pre-specified control rate of 20% ($p < 0.0001$; {Locke 2017}).

Refer to the current KTE-C19 IB for a summary of the safety and efficacy findings from this study.

2.8. KTE-X19-103 ZUMA-3 Phase 1 Experience

ZUMA-3 is a study of KTE-X19 in adults with r/r ALL (see Section 3). The DLT evaluation period of the study was completed with no DLTs observed in the 2 x 10^6 anti-CD19 CAR T cells/kg dose cohort. Additional subjects have been enrolled and treated in the phase 1 portion of the study at 1 x 10^6 anti-CD19 CAR T cells/kg and 0.5 x 10^6 anti-CD19 CAR T cells/kg. Forty-five patients were dosed in the Phase 1 portion of study across the 3 dose levels. Based on the risk-benefit ratio observed, the dose of 1 x 10^6 anti-CD19 CAR T cells/kg was considered the recommended Phase 2 dose.

Refer to the current KTE-X19 IB for a summary of the safety.

3. KTE-X19-103 STUDY DESIGN

3.1. General Study Design

ZUMA-3 is a Phase 1/2, multicenter, open-label study evaluating the safety and efficacy of KTE-X19 in adult subjects with relapsed or refractory B-precursor ALL. In this study, relapsed or refractory is defined as one of the following: primary refractory; first relapse following a remission lasting ≤ 12 months; relapsed or refractory after second-line or higher therapy; relapsed or refractory after allogenic SCT (provided the transplant occurred ≥ 100 days prior to enrollment and that no immunosuppressive medications were taken ≤ 4 weeks prior to enrollment).

During Phase 1, approximately 3-12 subjects with high burden [M3 marrow (>25% leukemic blasts) or ≥1000 blasts/mm^3 in the peripheral circulation] r/r ALL disease who are evaluable for DLT will be assessed to evaluate the safety of KTE-X19. A SRT that is internal to the study sponsor, and in collaboration with at least 1 study investigator, will review safety data and make recommendations regarding further enrollment in Phase 1 or proceeding to Phase 2 based on the incidence of DLTs and overall safety profile of KTE-X19. Additionally, approximately 40 subjects with high or low burden disease may be enrolled to further assess safety (see Figure 1 and Section 9.6).

During Phase 2, approximately 50 subjects in the mITT set will be assessed to evaluate the efficacy and safety of KTE-X19.

In total, up to approximately 100 subjects may be enrolled and treated with KTE-X19 in the study in Phase 1 and 2 combined (see Section 9.6 and Section 10.5).

During Phase 2, one interim and one primary analysis will be performed. The interim analysis is for safety only and will be performed by an independent DSMB after 20 Phase 2 subjects have been treated with KTE-X19 and had the opportunity to be followed for 30 days after the KTE-X19 infusion (see Section 10.7). Additional interim analyses for safety may be requested by the DSMB.

The primary analysis will occur when the overall study enrollment is complete and the last treated subject in the mITT set has had the opportunity to complete the month 6 disease assessment (see Section 10.8).

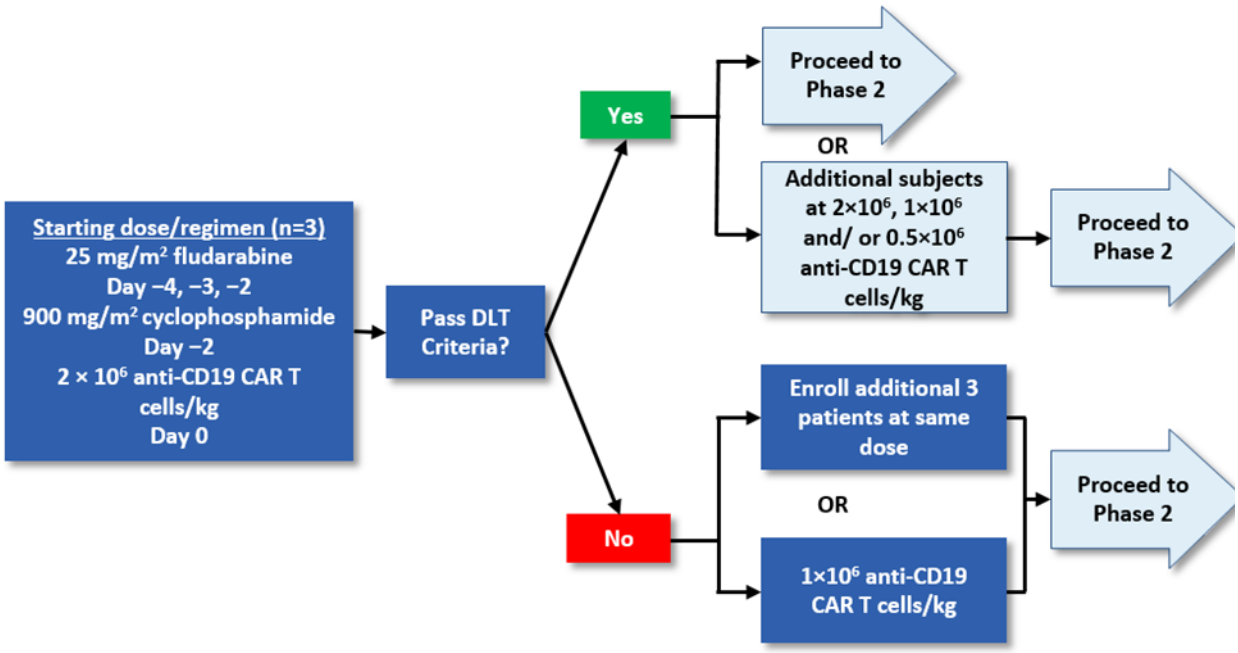
Each subject will provide consent and be evaluated for study participation. Once deemed eligible and enrolled into the study, each subject will follow the same study treatment schedule and procedural requirements, independent of the phase of the study, and proceed through the following study periods:

- Screening period
- Enrollment/Leukapheresis period
- Bridging chemotherapy and CSF prophylaxis period

- Conditioning chemotherapy period
- Investigational Product (IP) treatment period
- Post treatment assessment period
- Long term follow-up period

For study requirements assigned to each study period, refer to the schedule of assessments (SOA) and Section 7 for details. A study schema is drawn out and described at the end of the protocol synopsis section.

Figure 1. Phase 1 Dosing



3.2. Participating Sites

Approximately **35** centers located in North America, Europe, and potentially other regions will participate in this study. During the conduct of the study, additional regions, countries or sites may be added as necessary.

Sites that do not enroll a subject within 4 months of site activation may be considered for closure.

3.3. Number of Subjects

Participants in this trial will be referred to as "subjects". Up to approximately 100 subjects may be enrolled into the entire study in order to obtain 3-12 subjects evaluable for DLT in the Phase 1 portion, up to approximately 40 additional Phase 1 subjects, and approximately 50 subjects in the mITT set in the Phase 2 portion of the study.

It should be noted that Kite Pharma may choose to close enrollment at any time. Refer to the statistical considerations section of the protocol for sample size estimations.

3.4. Replacement of Subjects

Subjects will continue to be enrolled until the specified numbers of subjects are attained in the DLT evaluable (Phase 1) and mITT sets (Phase 2).

Subjects who have not received the required dose of KTE-X19 in order to be included in DLT evaluable set will be retained in the analyses of disposition and safety, where appropriate (see Section 10.5).

3.5. Study Duration

3.5.1. Study Duration for Individual Subjects

The duration of participation for individual subjects will vary depending on a subject's screening requirements, response to treatment, survival, and, if applicable, timing of transition to the separate Long-term Follow-up (LTFU) study, KT-US-982-5968 (refer to section 3.5.3).

The need for prolonged follow-up is based on the potential persistence of gene transfer vectors in treated subjects.

3.5.2. Completion of Study

Completion of the study is defined as the time at which every subject has completed at least 24 months of assessments, is considered lost to follow-up, withdraws consent, or dies. Upon activation of KT-US-982-5968 LTFU study at the subject's study site, subjects who received infusion of KTE-X19 will be offered the opportunity to complete LTFU assessments under the KT-US-982-5968 protocol.

3.5.3. Long-term Follow-up Period

All subjects who received an infusion of KTE-X19 will be provided the opportunity to transition to a separate LTFU study, KT-US-982-5968, where they will be monitored for occurrence of late-onset targeted AEs/SAEs suspected to be possibly related to KTE-X19 as defined in KT-US-982-5968, presence of replication-competent retrovirus (RCR) and/or insertional mutagenesis for up to 15 years from the time of KTE-X19 infusion (also refer to section 7.11.9)

In KT-US-982-5968, subjects will continue assessments at timepoints contiguous with the LTFU timepoints in this study.

4. SUBJECT SCREENING AND ENROLLMENT

All subjects must sign and date the IRB/IEC approved consent form before initiating any study specific procedures or activities that are not part of a subject's routine care. Refer to Section 7 for details.

Each subject who enters the screening period will receive a unique subject identification number at the time of consent [refer to the Investigational Product Manual (IPM)]. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject.

Furthermore, the subject identification number must remain constant throughout the entire clinical study, it must not be changed after enrollment or if the subject is rescreened.

Once a subject commences leukapheresis, the subject will be considered enrolled into the study.

5. SUBJECT ELIGIBILITY

5.1. Inclusion Criteria

101) Relapsed or refractory B-precursor ALL defined as one of the following:

- Primary refractory disease
- First relapse if first remission ≤ 12 months
- Relapsed or refractory disease after two or more lines of systemic therapy
- Relapsed or refractory disease after allogeneic transplant provided subject is at least 100 days from stem cell transplant at the time of enrollment and off of immunosuppressive medications for at least 4 weeks prior to enrollment

102) Morphological disease in the bone marrow (> 5% blasts)

103) Subjects with Ph^+ disease are eligible if they are intolerant to tyrosine kinase inhibitor (TKI) therapy, or if they have relapsed/refractory disease despite treatment with at least 2 different TKIs

104) Age 18 or older

105) Eastern cooperative oncology group (ECOG) performance status of 0 or 1

106) ANC ≥ 500/μL unless in the opinion of the PI cytopenia is due to underlying leukemia and is potentially reversible with leukemia therapy

107) Platelet count ≥ 50,000/μL unless in the opinion of the PI cytopenia is due to underlying leukemia and is potentially reversible with leukemia therapy

108) Absolute lymphocyte count ≥ 100/μL

109) Adequate renal, hepatic, pulmonary and cardiac function defined as:

- Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 cc/min
- Serum ALT/AST ≤ 2.5 x ULN (upper limit normal)
- Total bilirubin ≤ 1.5 mg/dl, except in subjects with Gilbert's syndrome.
- Left ventricular ejection fraction (LVEF) ≥ 50%, no evidence of pericardial effusion as determined by an ECHO, no NYHA class III or class IV functional classification, and no clinically significant arrhythmias
- No clinically significant pleural effusion
- Baseline oxygen saturation > 92% on room air

110) Females of childbearing potential must have a negative serum or urine pregnancy test

111) In subjects previously treated with blinatumomab, CD19 tumor expression on blasts obtained from bone marrow or peripheral blood must be documented after completion of the most recent prior line of therapy. If CD19 expression is quantified, then blasts must be ≥ 90% CD19 positive.

5.2. Exclusion Criteria

201) Diagnosis of Burkitt's leukemia/lymphoma according to WHO classification or chronic myelogenous leukemia lymphoid blast crisis

202) History of malignancy other than non-melanoma skin cancer or carcinoma in situ (eg, cervix, bladder, breast) unless disease free for at least 3 years

203) History of severe hypersensitivity reaction to aminoglycosides or any of the agents used in this study

204) CNS abnormalities

- Presence of CNS-3 disease defined as detectable cerebrospinal blast cells in a sample of CSF with ≥ 5 WBCs per mm^3 with or without neurological changes, and
- Presence of CNS-2 disease defined as detectable cerebrospinal blast cells in a sample of CSF with <5 WBCs per mm^3 with neurological changes
  Note: Subjects with CNS-1 (no detectable leukemia in the CSF) and those with CNS-2 without clinically evident neurological changes are eligible to participate in the study.
- History or presence of any CNS disorder such as a seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, any autoimmune disease with CNS involvement, posterior reversible encephalopathy syndrome (PRES), or cerebral edema

205) History of concomitant genetic syndrome associated with bone marrow failure such as Fanconi anemia, Kostmann syndrome, Shwachman-Diamond syndrome

206) History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months of enrollment

207) History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months of enrollment.

208) Primary immunodeficiency

209) Known infection with HIV, hepatitis B or hepatitis C virus. A history of hepatitis B or hepatitis C is permitted if the viral load is undetectable per quantitative PCR and/or nucleic acid testing.

210) Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring antimicrobials for management. Simple UTI and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the Kite Medical Monitor

211) Prior medication:

- Salvage systemic therapy (including chemotherapy, TKIs for Ph^+ ALL, and blinatumomab) within 1 week or 5 half-lives (whichever is shorter) prior to enrollment
- Prior CD19 directed therapy other than blinatumomab
- History of CTCAE grade 4 neurologic event or grade 4 CRS {Lee 2014} with prior CD19-directed therapy
- Treatment with alemtuzumab within 6 months prior to enrollment, clofarabine or cladribine within 3 months prior to enrollment, or PEG-asparaginase within 3 weeks prior to enrollment
- Donor lymphocyte infusion (DLI) within 28 days prior to enrollment
- Any drug used for GVHD within 4 weeks prior to enrollment (eg, calcineurin inhibitors, methotrexate, mycophenolyate, rapamycin, thalidomide), or immunosuppressive antibody used within 4 weeks prior to enrollment (eg, anti-CD20, anti-tumor necrosis factor, anti-interleukin 6 or anti-interleukin 6 receptor)
- At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy prior to enrollment (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists etc)
- Corticosteroid therapy at a pharmacologic dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to enrollment

212) Presence of any indwelling line or drain (eg, percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Ommaya reservoirs and dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted

213) Acute GVHD grade II-IV by Glucksberg criteria or severity B-D by IBMTR index; acute or chronic GVHD requiring systemic treatment within 4 weeks prior to enrollment

214) Live vaccine ≤ 4 weeks prior to enrollment

215) Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential

216) Subjects of both genders of child-bearing potential who are not willing to practice birth control from the time of consent through 6 months after the completion of KTE-X19

217) In the investigator's judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation

218) History of autoimmune disease (eg, Crohns, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years

6. PROTOCOL TREATMENT

6.1. Treatment Terminology

The following terms will be used to describe and define protocol treatment:

- Bridging chemotherapy refers to treatment used to control a subject's disease prior to conditioning chemotherapy.
- CSF prophylaxis will be administered prior to infusion of conditioning chemotherapy.
- The Conditioning chemotherapy regimen used for this study will be fludarabine and cyclophosphamide.
- The investigational product for this study is named KTE-X19.

6.2. Leukapheresis (within approximately 5 days of eligibility confirmation)

Before leukapheresis commences, the criteria outlined in Section 7.11.3 must be met.

Subjects will undergo leukapheresis to obtain leukocytes (white blood cells) for the manufacture of KTE-X19. Leukapheresed cells obtained from subjects at participating centers will be shipped to the Cell Processing Facility (CPF) overnight as described in the IPM.

Mononuclear cells will be obtained by leukapheresis (approximately 12-15 liter apheresis with a goal to target approximately 5-10 x 10^9 mononuclear cells). The leukapheresed cells are then packaged for expedited shipment to the CPF as described in the IPM.

Upon arrival at the CPF, each subject's leukapheresed product will be processed to positively select for T cells, which are then activated and transduced with a retroviral vector to introduce the CAR gene. The engineered T cells are then further expanded and cryopreserved to generate the investigational product per CPF standard operating procedures. After KTE-X19 has been manufactured and has passed release criteria, it will be shipped to the treating facility and must be stored per the IPM (see Section 6.6).

See Section 6.8 for excluded medications prior to leukapheresis.

6.3. Bridging Chemotherapy

Bridging therapy may be administered after leukapheresis and prior to conditioning chemotherapy at the investigators discretion. Bridging chemotherapy is recommended for all subjects particularly those subjects with high disease burden at baseline [M3 marrow (>25% leukemic blasts) or ≥ 1000 blasts/mm^3 in the peripheral circulation]. If prescribed, bridging chemotherapy must be administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy.

Allowed bridging chemotherapy regimens are outlined in Table 2. Doses listed are recommended, and can be adjusted for age/comorbidities or per local or institutional guidelines.

Table 2. Bridging Chemotherapy Regimens

Bridging Chemotherapy Regimen [a]	
Attenuated VAD: Vincristine non-liposomal (1-2 mg IV weekly) or liposomal (2.25 mg/m^2 IV weekly), and dexamethasone 20-40 mg IV or PO daily x 3-4 days per week. Optional doxorubicin 50 mg/m^2 IV x 1 (first week only).	DOMP: Dexamethasone 6 mg/m2/day PO (or IV) divided BID days 1-5, vincristine 1.5 mg/m2 (maximum dose 2 mg) IV on day 1, methotrexate 20 mg/m2 PO weekly, 6-MP 50-75mg/m2/day PO daily
Mercaptopurine (6-MP): 50-75 mg/m^2/day by mouth (administer at bedtime on an empty stomach to improve absorption)	Attenuated FLAG/FLAG-IDA: fludarabine 30 mg/m^2 IV days 1-2, cytarabine 2 g/m^2 IV days 1-2, G-CSF 5 µg/kg SC or IV starts on day 3 and can continue until day before the start of conditioning chemotherapy. With or without idarubicin 6 mg/m^2 IV days 1-2.
Hydroxyurea: Doses titrated between 15-50 mg/kg/day (rounded to the nearest 500 mg capsule and given as a single daily oral dose on a continuous basis)	Mini-hyper CVAD (courses A and/or B): Course A: Cyclophosphamide 150 mg/m^2 q 12 hrs x 3 days, dexamethasone 20 mg/d IV or PO daily days 1-4 and 11-14, vincristine 2 mg IV x 1 Course B: methotrexate 250 mg/m^2 IV over 24h on day 1, cytarabine 0.5 g/m^2 IV q12h x 4 doses on days 2 and 3.

a Use of a TKI in combination with any of the above regimens is allowed for subjects with Ph$^+$ ALL and Ph-like ALL

Given subjects with r/r ALL can have rapidly progressive disease and clinical deterioration, bridging chemotherapy allows physicians to provide standard of care to subjects in the period between leukapheresis and manufacturing of KTE-X19. Based on the published data {Davila 2014, Lee 2014, Maude 2014}, decreased tumor burden is additionally associated with less cytokine release syndrome (CRS).

Bridging therapy should be administered per institutional guidelines.

Refer to the current product label for guidance on packaging, storage, preparation, administration, including necessary dose reductions for organ dysfunction, and toxicity management associated with the administration of chemotherapy agents.

6.4. CSF Prophylaxis

All subjects will receive CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines (eg, methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, or dexamethasone 4 mg or equivalent steroid dose).

CSF prophylaxis will be administered any time during screening (eg, at time of screening lumbar puncture) through 7 days prior to KTE-X19 infusion.

Subjects who are enrolled with CNS-2 disease at baseline must receive CSF prophylaxis after leukapheresis and at least 7 days prior to KTE-X19 infusion, unless otherwise approved by the Kite Medical Monitor.

Multiple doses of CSF prophylaxis can be given per investigator discretion in accordance with institutional guidelines, but at least 7 days must pass between the last dose of CSF prophylaxis and KTE-X19 infusion.

Additional CSF prophylaxis may be given post-KTE-X19 infusion per investigator discretion in accordance with institutional guidelines, but should be avoided for at least 8 weeks after KTE-X19 infusion if possible.

Should a subject have an Ommaya reservoir and there is no evidence of blockage of CSF flow from the spinal canal, administration of CSF prophylaxis through the reservoir is acceptable.

6.5. Conditioning Chemotherapy

Conditioning chemotherapy refers to fludarabine and cyclophosphamide used for lymphodepletion prior to administration of KTE-X19. Subjects will receive conditioning chemotherapy from Day -4 through day -2.

Conditioning chemotherapy will be supplied by the investigative site unless otherwise noted.

Refer to the current product label for guidance on packaging, storage, preparation, administration and toxicity management associated with the administration of chemotherapy agents.

The investigational medicinal product (KTE-X19) must be available before initiation of conditioning chemotherapy.

See Section 7.11.6.1 for conditioning chemotherapy procedures.

6.5.1. Fludarabine

Fludarabine phosphate is a synthetic purine nucleoside that differs from physiologic nucleosides in that the sugar moiety is arabinose instead of ribose or deoxyribose. Fludarabine is a purine antagonist antimetabolite.

6.5.2. Cyclophosphamide

Cyclophosphamide is a nitrogen mustard-derivative alkylating agent. Following conversion to active metabolites in the liver, cyclophosphamide functions as an alkylating agent; the drug also possesses potent immunosuppressive activity. The serum half-life after IV administration ranges from 3-12 hours; the drug and/or its metabolites can be detected in the serum for up to 72 hours after administration.

6.5.3. Mesna

Mesna is a detoxifying agent used to inhibit the hemorrhagic cystitis induced by chemotherapy. The active ingredient in mesna is a synthetic sulfhydryl compound designated as sodium-2-mercaptoethane sulfonate with a molecular formula of $C_2H_5NaO_3S_2$. Mesna will be administered around the cyclophosphamide dose according to institutional standards.

6.5.4. Rationale for Conditioning Chemotherapy Choice and Dose

The rationale for the conditioning chemotherapy regimen and dose selection is based on the Phase 1 study conducted at the Pediatric Oncology Branch at the NCI {Lee 2015}. In this study, 21 subjects (20 with ALL) were treated and all received the same fludarabine and cyclophosphamide schedule with a favorable benefit/risk profile.

Consistent with the NCI protocol {Lee 2015}, the KTE-X19-103 study will use the same Conditioning chemotherapy regimen consisting of fludarabine at a dose of 25 mg/m^2/day IV over 30 minutes on Day -4, Day -3, Day -2 prior to KTE-X19 and cyclophosphamide at a dose of 900 mg/m^2/day IV over 60 minutes on Day -2 prior to KTE-X19. Day -1 will be a rest day. The 3-day conditioning chemotherapy regimen may be administered in an outpatient setting in accordance with the daily dosing instructions outlined in Section 7.11.6.2.

Following completion of each subjects' conditioning chemotherapy regimen, subjects will receive their respective KTE-X19 infusion.

6.6. KTE-X19

The IP for this study is KTE-X19.

Refer to the most current Investigator's Brochure regarding KTE-X19 and clinical experience. This section contains general information and is not intended to provide specific instructions. Refer to the IPM for details and instruction on storage and administration of KTE-X19.

KTE-X19 is supplied cryopreserved in cryostorage bags. The product in the bag is slightly cloudy, with cream to yellow color. The cryostorage bags containing KTE-X19 arrive frozen in a liquid nitrogen dry shipper. The bags must be stored in vapor phase of liquid nitrogen and the product remains frozen until the subject is ready for treatment to assure viable live autologous cells are administered to the subject. Several inactive ingredients are added to the product to assure viability and stability of the live cells through the freezing, thawing, and infusion process.

KTE-X19 is a subject-specific product and the intended subject will be identified by a unique subject ID number. Upon receipt, verification that the product and subject-specific labels match the subject's information (eg, initials, subject ID number) is essential. Do not infuse the product if the information on the subject-specific label does not match the intended subject. The volume of KTE-X19 infused, the thaw start/stop time, and KTE-X19 infusion start/stop time, will be noted in the subject medical record. The product must not be thawed until the subject is ready for the infusion.

To date, subjects have received doses of anti-CD19 CAR T cells ranging from 0.5 - 30 x 10^6 anti-CD19 CAR T cells/kg. There have been no instances of accidental overdose of subjects in this program. In case of accidental overdose, treatment should be supportive. Corticosteroid therapy may be considered if any dose is associated with severe toxicity (see Section 6.8 for more information related to corticosteroid use).

6.6.1. Rationale for KTE-X19 Dose

The rationale for the initial dose of KTE-X19 evaluated in ZUMA-3 (2 x 10^6 anti-CD19 CAR T cells/kg) was based on the DLT and MTD data generated from the 2 studies conducted at the Pediatric Oncology {Lee 2015} and Surgery Branch {Kochenderfer 2015} of the NCI. Additional doses evaluated in this study are further informed by emerging Phase 1 data (see Section 2.8).

In the Pediatric Oncology Branch study, 4 pediatric subjects were enrolled and received a starting dose of 1 x 10^6 anti-CD19 CAR T cells/kg with no DLT observed. The CAR T cell dose was then escalated to 3 x 10^6 anti-CD19 CAR T cells/kg. At this higher dose, 4 pediatric subjects were treated and 2 subjects experienced a CRS DLT (one Grade 3 and one Grade 4 event). Based on these observations, the study defined the MTD at 1 x 10^6 anti-CD19 CAR T cells/kg for the remainder of the study.

In the Surgery Branch adult study, as of November 30, 2014, Group 3 enrolled 11 adult subjects, where the first 7 and last 4 subjects received anti-CD19 CAR T cell infusion of 1 x 10^6 anti-CD19 CAR T cells/kg and 2 x 10^6 anti-CD19 CAR T cells/kg, respectively and the benefit/risk profile remained favorable.

In the ZUMA-3 study, the initial 6 subjects were treated at 2 x 10^6 anti-CD19 CAR T cell/kg, with a subsequent group of 14 subjects treated at 1 x 10^6 anti-CD19 CAR T cell/kg. No DLTs were observed in the DLT evaluable set, no drop off was seen in efficacy between the 2 x 10^6 anti-CD19 CAR T cell/kg and 1 x 10^6 anti-CD19 CAR T cell/kg KTE-X19 doses, and there was no clear difference in the safety profile (Section 2.8; {Shah 2016}). These data suggested it may be possible to lower the KTE-X19 dose further without diminishing and potentially enhancing the risk:benefit profile of KTE-X19 in r/r ALL. As a result, additional subjects were dosed at 0.5 x 10^6 anti-CD19 CAR T cells/kg. The safety profile observed at the lower dose was considered manageable, however the efficacy was diminished compared to higher dose levels. Based on the safety/efficacy observations, the SRT decision was to explore the safety profile at the 1 x 10^6 anti-CD19 CAR T cell/kg with implementation of new toxicity management recommendations by enrolling additional subjects at this dose level. The new safety profile observed at the dose of 1 x 10^6 anti-CD19 CAR T cell/kg was considered favorable without significant decrease in efficacy, therefore the dose of 1 x 10^6 anti-CD19 CAR T cell/kg was considered the recommended Phase 2 dose.

For subjects weighing greater than 100 kg, a maximum flat dose of 2 x 10^8 or 1 x 10^8 or 0.5 x 10^8 anti-CD19 CART cells may be administered. See Sections 9.6 for details. If any problems related to the use of KTE-X19 or any products that support the successful delivery and infusion of KTE-X19 (eg, cryostorage bags, subject identification labels) required in this study are identified, refer to the instructions in the IPM for details).

6.7. Concomitant Therapy

Concomitant therapy refers to treatment that subjects receive during the conduct of the study.

Investigators may additionally prescribe any other concomitant medications or treatment deemed necessary to provide adequate supportive care, including growth factor support (eg, G-CSF) and routine anti-emetic prophylaxis and treatment except those medications listed in the excluded medication Section 6.8.

In subjects with Ph^+ disease and who achieve **CR**, a TKI may be resumed 2 months after KTE-X19 infusion at the investigator discretion and in accordance with institutional guidelines. See Section 3, Table 2 for use of TKI's during bridging chemotherapy.

The investigator is responsible for reporting all concomitant medications as follows in Table 3:

Table 3. Reporting Requirements for Concomitant Medications

Subjects who are pre-screen or screen-fails	Subjects who are enrolled, but do not receive KTE-X19 infusion	Subjects who are enrolled and receive KTE-X19 infusion
• Concomitant therapies related to serious adverse event(s) will be recorded from the date of the pre-screening informed consent or screening informed consent through 30 days after the last study-specific pre-screening or screening procedure, respectively.	• Concomitant therapies will be recorded from the date of the informed consent until 30 days after the last study-specific procedure has occurred (eg, leukapheresis, conditioning chemotherapy) or until the initiation of new anti-cancer therapy, whichever occurs first.	• Concomitant therapies including medications, intubation, dialysis, oxygen, and blood products will be recorded from the date of the informed consent until 3 months after completing treatment with KTE-X19. (excluding allogeneic SCT) • After this 3-month follow-up period, targeted concomitant therapies will be recorded for either 24 months after KTE-X19 infusion or until disease progression, whichever occurs first. o Targeted concomitant therapies include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations. o In subjects who received allogeneic SCT, only concomitant medications related to a KTE-X19-related serious adverse event (SAE) will be recorded. Reporting of these concomitant medications will commence at the time the SCT preparative regimen commences.

See Section 6.9 regarding documentation of subsequent anticancer therapy.

6.8. Excluded Medications

Corticosteroid therapy at a pharmacologic dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis and 5 days prior to KTE-X19 infusion.

Systemic corticosteroids should be avoided as premedication in subjects for whom CT scans with contrast are contraindicated (ie, subjects with contrast allergy or impaired renal clearance). If possible, such subjects should undergo non-contrast CT scans or alternative imagine modality (such as MRI) instead.

Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after KTE-X19 infusion, unless used to manage KTE-X19 related toxicities (Refer to the most current version of the IB; see Section 6.4). Other medications which may interfere with evaluation of KTE-X19, such as non-steroidal anti-inflammatory agents should also be avoided for the same time period unless medically necessary.

Therapeutic doses of systemic anticoagulants, such as unfractionated heparin and low-molecular weight heparin, should be avoided anytime subjects are at risk of bleeding due to thrombocytopenia when possible. If a subject requires the initiation of therapeutic anticoagulant doses prior to initiation of conditioning chemotherapy or prior to KTE-X19 infusion, then conditioning chemotherapy/KTE-X19 infusion must be held and the case discussed with the Kite Medical Monitor.

For subjects with Ph^+ ALL, all TKIs must be stopped at least 1 week prior to KTE-X19 infusion, including but not limited to imatinib, dasatinib, and ponatinib. In subjects who achieve CR, a TKI may be resumed 2 months after KTE-X19 infusion. See Section 6.3, Table 2 for use of TKIs during bridging chemotherapy.

CSF prophylaxis may be given post-KTE-X19 infusion per investigator discretion in accordance with institutional guidelines, but should be avoided for at least 8 weeks after KTE-X19 infusion if possible.

Treatment for the subject's leukemia such as chemotherapy, immunotherapy, targeted agents, radiation, high dose corticosteroid, other than defined/allowed in this protocol, and other investigational agents are prohibited except as needed for treatment of disease progression after KTE-X19 infusion. If permissibility of a specific medication/treatment is in question, contact the Kite Pharma medical monitor.

Medications with sedative properties should be avoided if possible in the setting of neurologic events (refer to the KTE-X19 IB).

6.9. Subsequent Therapy

Subsequent therapy administered after KTE-X19 infusion for a subject's disease such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy will be recorded for all enrolled subjects until one of the following occurs: subject completes the long-term follow-up period, is considered lost to follow-up, withdraws consent, dies, or transitions to the KT-US-982-5968 LTFU study where subsequent therapy will continue to be recorded.

For subjects who are enrolled, but do not receive KTE-X19 infusion, any additional anti-cancer therapy will also be collected until the subject completes their participation in the current study, is considered lost to follow up, withdraws consent, or dies, whichever occurs first.

6.10. Toxicity Management

To date, the following important risks have been identified with KTE-X19: CRS, neurological events, infections, and cytopenias. Refer to the current KTE-X19 IB for details regarding these events and management guidance.

As the safety experience with KTE-X19 increases, the management guidance may be updated. Therefore, it is important that you always refer to the most current version of the KTE-X19 IB for guidance regarding managing KTE-X19 related toxicities.

Additional information and management recommendations can also be found in the IB regarding important potential risks associated with KTE-X19 as well as possible complications associated with malignancy and cancer treatment.

7. STUDY PROCEDURES

Research staff should refer to the SOA for an outline of the procedures required. The visit schedule is calculated from KTE-X19 infusion on Day 0.

An overview of study assessments/procedures is outlined below. A description for each period of the study is provided in Section 7.11. Refer to the CRF completion guidelines for data collection requirements and documentation of study procedures.

7.1. Informed Consent

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the study design, anticipated benefits and the potential risks. Subjects should sign the most current Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved Informed Consent form (ICF) prior to any study specific activity or procedure is performed.

The consent process and the subject's agreement or refusal to participate in the study is to be documented in the subject's medical records. If the subject agrees to participate, the ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF will be retained in accordance with institution policy and IRB/IEC requirements with a copy of the ICF provided to the subject.

All subjects who are enrolled into the study should be re-consented with any updated version of the IRB/IEC approved ICF if relevant to their participation in the study.

7.2. Demographic Data

Demographic data will be collected per country and local regulations and guidelines. Where applicable, demographic data will include sex, year of birth, race, ethnicity and country of enrollment to study their possible association with subject safety and treatment effectiveness.

7.3. Medical and Treatment History

Relevant medical history prior to the start of adverse event reporting will be collected. Relevant medical history is defined as data on the subject's concurrent medical condition that would be typically shared in a referral letter. All findings will be recorded in the CRFs.

In addition to the medical history, all history related to the subject's disease, treatment and response to treatment will be collected and must date back to the original diagnosis.

For subjects who are being referred from another clinic or institution to the participating research center, copies from the subject's chart should be obtained.

7.4. Physical Exam, Vital Signs, Performance Status, and European Quality of Life-5 Dimensions (EQ-5D)

Physical exams will be performed during screening and at times noted in the SOA. Changes noted in subsequent exams when compared to the baseline exam will be reported as an adverse event.

During KTE-X19 infusion/hospitalization, vital signs including blood pressure, heart rate, oxygen saturation, and temperature will be monitored before and after the KTE-X19 infusion and then routinely (every 4-6 hours) while hospitalized. If the subject has a fever (temperature 38.3^{o}C or greater) at any time during hospitalization, vital signs will be monitored more frequently as clinically indicated.

Performance status as measured by the ECOG scale will be performed to quantify the subject's general well-being and ability to perform activities of daily life.

The EQ-5D will be completed only for subjects participating in phase 2. The EQ-5D will be completed at the timepoints outlined in the SOA prior to other study related procedures or assessments. Subjects who are blind or illiterate may have the EQ-5D questions read to them by the study staff. The study staff, however, cannot interpret any of the questions for the subject. A subject may be exempt from completing the questionnaire if he or she is unable to read the questionnaire in one of the country languages available.

The EQ-5D is a 2 page generic patient questionnaire for assessing the overall health status of a subject. The EQ-5D consists of a 5 dimension descriptive system including questions on mobility, self-care, usual activities, pain/comfort, and anxiety/depression and a visual analogue scale (EQ VAS) which allows the respondent to record health on a vertical scale (eg, best health to worst health) thus allowing a quantitative measure of health outcome.

7.5. Neurological Assessment

Subject's neurological status should be evaluated at screening to establish a baseline. After enrollment, subjects should be evaluated for any neurological symptoms at each of the timepoints specified in the SOA. During the hospitalization period, evaluations of neurological status may need to be increased. Changes in neurological status should be reported as an adverse event per Section 9.

7.6. Cardiac Function

Each subject's cardiac function as measured by ECHO will be assessed during the screening period to confirm study eligibility. No evidence of pericardial effusion, as required by eligibility, will also be confirmed by ECHO.

If the last chemotherapy regimen the subject received is not considered cardiotoxic, then an ECHO performed within 28 days prior to signing the consent may be used for eligibility.

If the last chemotherapy regimen the subject received is considered cardiotoxic, then an ECHO performed following the subjects last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility.

A baseline chest x-ray will be completed within 14 days before enrollment to confirm eligibility.

To establish a baseline, an ECG will be performed within 30 days before enrollment.

7.7. Lumbar Puncture

CSF samples (ie, collected on or after informed consent) will be analyzed locally for disease assessment (see Section 7.8 for details regarding analytes). A portion will be submitted to the central laboratory for disease assessment and toxicity evaluation. Refer to refer to the KTE-X19 IB regarding platelet support.

Should a subject have an Ommaya reservoir and there is no evidence of blockage of CSF flow from the spinal canal, withdrawal of the CSF sample through the reservoir is acceptable.

CSF samples will be collected at the following time points:

- Baseline – a CSF result obtained within 30 days before enrollment will be acceptable for eligibility determination
- At the time of CSF prophylaxis (this sample may be the same as the baseline sample)
- For subjects with CNS-2 at baseline, a CSF sample is required at the time of first presumed response (ie, bone marrow blasts < 5%)
- First onset of ≥ grade 2 neurological symptoms or as medically indicated
- Additional evaluations of the CSF should be performed per institutional standard of care

CSF blast counts can be falsely increased in cases of traumatic lumbar puncture. In this instance, the blast count should be adjusted using the following formula, and the corrected value entered into the CRF:

$$blast(CSF, true) = blast\ (CSF, observed) - blast\ (blood)\ \times \frac{RBC(CSF)}{RBC(blood)}$$

Subjects with CNS-2 will have a lumbar puncture performed at the screening visit for examination of CSF. In addition, a lumbar puncture may be performed as applicable for subjects with new onset of a Grade 2 or higher neurologic event after KTE-X19 infusion

7.8. Laboratory

The below samples will be collected at the time points indicated in the SOA. Additional samples (eg, blood, urine, other bodily fluids, tissue) may be collected as needed for further safety testing.

Local Laboratory Analysis:

- Bone marrow evaluation for % blasts
- Cerebral spinal fluid (total protein, WBC, RBC, %blast by morphological assessment, and gram stain and culture if clinically indicated or for neurological event)
- Sodium (Na), Potassium (K), Chloride (Cl), Total CO_2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN) or Urea (if BUN not available), Albumin, Calcium (Ca) total, Magnesium total (Mg), Inorganic Phosphorus (P), Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LDH, Uric Acid (Note: Direct Bilirubin, LDH, and Uric Acid are recommended, not mandatory)
- C-reactive protein
- Complete Blood Count with differential (5-part preferred, but 3-part will be acceptable)
- Peripheral blast count recommended (see Section 7.11.6.3 regarding Day -4)
- Absolute lymphocyte count (ALC)
- CD3 count based on peripheral blood
- CD19 immunophenotyping by flow cytometry or IHC using peripheral blood or bone marrow
  - Note: Surface CD19 expression should be measured by flow cytometry; IHC analysis is allowed if the bone marrow aspirate is a dry tap, inadequate or there were insufficient circulating blasts for flow cytometry.
- A urine or serum sample will be collected for females of childbearing potential. If the screening pregnancy test is positive, the subjects should not be enrolled. If a standard of care pregnancy test is collected during the course of the study, and the result is positive, the investigator should contact the Kite Pharma medical monitor for instructions. If a female partner of a male subject becomes pregnant during the conduct of the study, it must be reported by contacting Kite Pharma Medical Monitor for instructions.
- For European Union (EU) sites, viral serologic tests (eg, HIV, hepatitis B, hepatitis C) will be carried out per institution guidelines and EU regulations. This may be done within the 30 days prior to leukapheresis and/or on the day of leukapheresis (see Section 7.11.1).

Central Laboratory Analysis:

- Bone marrow biopsy and aspirate samples collected for confirmation of diagnosis as well as disease assessment
- Cerebral spinal fluid

- Blood draws for cytokine levels and PBMCs (for the analysis of lymphocyte subsets, anti-CD19 CART cells, and replication-competent retrovirus [RCR] analysis)
- Serum samples will also be drawn for anti-KTE-X19 antibodies
- Peripheral blood
- See central laboratory manual for details.

7.9. Disease Assessments

7.9.1. Bone Marrow Evaluation

Bone marrow aspirates and biopsies will be collected throughout the study per the protocol SOA and/or standard of care.

- Screening bone marrow evaluation:
  - If available, archival formalin-fixed paraffin embedded (FFPE) bone marrow block and/or slides used for the original diagnosis of ALL will be submitted to the central laboratory along with the pathology report.
  - A bone marrow aspirate and biopsy is required at screening and will be performed after the last dose of systemic chemotherapy and within approximately 14 days before enrollment to establish baseline disease.
    - If there is a delay between when the screening bone marrow is performed and the apheresis, contact the Kite Medical Monitor for guidance on whether or not bone marrow evaluation needs to be repeated. If a fresh bone marrow aspirate and biopsy was recently collected and properly stored prior to consent, then contact the Kite Medical Monitor to confirm if this sample is adequate for screening.
  - In subjects who receive bridging chemotherapy, an additional bone marrow sample is required between the end of bridging chemotherapy and Day -4. If bridging chemotherapy is not administered, then the additional bone marrow sample is not required, however, an assessment of peripheral circulating blasts is required (see Section 7.11.6.3 regarding requirement for peripheral blast count).
- On study bone marrow evaluations:
  - A bone marrow aspirate will be required at all time points per the SOA to assess treatment response.
    - For subjects who undergo a SCT, bone marrow evaluations are not required during the first 100 days post-SCT. After 100 days, bone marrow evaluations should be performed at the next per protocol time point per the SOA. If a subject has a bone marrow evaluation earlier than the next per protocol time point, then the bone marrow samples should be processed and submitted to the central laboratory per the central laboratory manual.

- In addition to the bone marrow aspirate, a bone marrow biopsy is required at Day -4 and Day 28. A bone marrow biopsy at all other time points is recommended and should be performed if standard of care. Note: Anytime the bone marrow aspirate is a dry tap, then a bone marrow biopsy is required. In the case of a dry tap, the bone marrow biopsy will be used to determine disease burden by immunohistochemical (IHC) analyses. The following markers will be analyzed by IHC: CD10, CD19, CD20, CD34, Pax5 and TdT.

- For subjects who sign the optional portion of the consent form, a Day 7 bone marrow biopsy and aspirate will be performed. The optional day 7 bone marrow may be performed between day 7 and 14.

- Reminders:

  - For subjects with a CR, collection and analysis of CSF is required to confirm CR (see Section 7.7)

  - For subjects with PD, a PBMC sample should be collected at time of progression and prior to starting subsequent anticancer therapy

Locally evaluated % blasts from the bone marrow evaluation and if available local MRD will be entered to the CRF.

Overall response will be assessed by the investigator per Appendix 1. If bone marrow blasts are ≤ 5% and circulating blasts are ≥ 1%, then additional studies (eg, flow cytometry) should be performed to quantify the blasts.

Bone marrow aspirate and biopsy samples will be processed and submitted to the central laboratory as outlined in the central laboratory manual. Refer to the laboratory manual for collection, processing and shipment requirements; note some samples, eg, MRD, must be shipped on the same day of collection. Below is an overview of the sample types that will be required.

Samples from bone marrow aspirate may include:

- MRD assessment

- Stained slide smears

  - The same slides used to evaluate ALL disease status (eg, % blasts) locally will be submitted to the central laboratory and will then be returned back to the investigative site after the review is completed. If the same slides used to diagnose ALL cannot be submitted to the central laboratory per institutional policy, then slides from the same procedure should be submitted. See central laboratory manual for details.

- Bone marrow mononuclear cells

Samples from bone marrow biopsy may include:

- Touch prep slide
- Core biopsy in formalin, formalin-fixed paraffin embedded block, or unstained slides

The corresponding pathology report should be submitted to the central laboratory along with the archival and on-study bone marrow samples.

7.9.2. Imaging Requirements (Only Applies to Subjects with Known Non-CNS Extramedullary Disease at Baseline)

- Extramedullary disease will be assessed prior to baseline with an imaging modality appropriate for the anatomical site and clinical scenario (eg, MRI for CNS lesion, ultrasound for testicular lesion, CT for intra-abdominal or thoracic lesion).
  - For all subjects with known non-CNS extramedullary disease, images must be taken within 28 days before conditioning chemotherapy. In addition, for subjects receiving bridging chemotherapy, images must be taken after bridging chemotherapy has completed.
- Following KTE-X19 infusion, the first on study images will occur at the time of first presumed response (ie, bone marrow blasts ≤ 5%)
- Subsequent images will continue as per the SOA through Month 24 or disease progression, whichever occurs first. If the subject's disease has not progressed by Month 24, then images will be performed per standard of care until disease progression.
- All on-study assessments of extramedullary disease detected through imaging should be made with the same imaging modality and of the same anatomical locations as imaged at baseline.
- Response is evaluated by the investigator (Appendix 1).
- For all subjects, images should be performed per standard of care anytime the subject presents with symptoms suggestive of disease progression even if it is off schedule as per the SOA.
- Images will be submitted to a central imaging vendor; central imaging vendor manual to be provided separately.

7.10. Biomarkers

Biomarker analysis will be performed on blood and bone marrow derived tumor samples to evaluate predictive and pharmacodynamic markers for KTE-X19. Prognostic markers specific for B-ALL and related to the tumor immune environment may also be evaluated.

The presence, expansion, persistence, and immunophenotype of transduced anti-CD19 CAR T cells will be monitored in the blood and bone marrow by flow cytometry. Expansion and persistence in peripheral blood will also be monitored by a CD19 CAR specific droplet digital chain reaction assay (ddPCR).

Levels of serum cytokines and chemokines will be evaluated in the blood and CSF. The analysis of cytokines and chemokines in the CSF will be performed at baseline and post-anti-CD19 CAR T cell infusion in subjects who present with first onset of ≥ grade 2 neurologic events. An additional sample for serum cytokine and chemokine analysis should be drawn at first onset and first reoccurrence of any > grade 2 CRS (per Lee 2014 criteria; Table 15) if not already collected on that day. The following cytokines may be included in the panel: pro-inflammatory and immune modulating cytokines IL-6, TNFα, IL-8, IL-1, IL-2, GM-CSF, IL-15, IL-17a, IFNγ, IL-12p40/p70; immune effector molecules Granzyme A, B, Perforin, sFasL; correlates of acute phase response C-reactive protein (CRP), SAA and Chemokines MIP-1α, MIP-3α, IP-10, Eotaxin, MCP-4.

Cerebrospinal fluid (CSF) as well as any additional subject samples (eg, pleural fluid) may be collected from subjects who develop neurologic events or CRS to enable evaluation of inflammatory cytokines and chemokine levels. As applicable lymphocyte populations residing in the CSF or other additional subject samples may also be analyzed for the purpose of understanding the safety profile of KTE-X19.

As KTE-X19 comprises retroviral vector transduced T cells, the presence of RCR in the blood of treated subjects will be monitored. Replication-competent retrovirus testing will occur at baseline, Month 3, Month 6, and Month 12. Thereafter, samples will be collected yearly and held for up to 15 years. If a subject tests positive for RCR at any time point within the first year, samples will continue to be collected and tested yearly for up 15 years or as clinically indicated. Baseline leukapheresis and final KTE-X19 samples will be banked and may be analyzed by immunophenotyping, quantitative polymerase chain reaction (qPCR) and/or gene expression profiling. Remaining samples may be stored for future exploratory analysis of immune related DNA, RNA, or protein markers.

A pre-treatment bone marrow aspirate and biopsy will be collected for central pathology review, establishment of baseline protein and molecular markers for subsequent MRD assessment and evaluation of prognostic markers specific for B-ALL and also the tumor immune environment. Additional analysis may include CD19 expression, gene expression profiling, and analysis of DNA alterations. Remaining tumor samples may be stored for future exploratory analysis of DNA (somatic mutations), RNA, or protein markers.

Monitoring of MRD to determine presence of residual leukemic blasts will be performed on bone marrow aspirates**.** Standard assessment of MRD utilizing multicolor flow cytometry or qPCR to detect residual cancerous cells with a sensitivity of 10^{-4}, will be accompanied by a more sensitive analysis utilizing next generation sequencing with a sensitivity of 10^{-6}. The latter detects clonal B-cell specific sequences that are shared across the malignant cell population. Given that clinical correlates of MRD status in B-ALL are based on a threshold of 10^{-4}, and clinical significance of identifying blasts at the 10^{-6} level is uncertain, the higher sensitivity analysis is for exploratory purposes only and will not be used to derive the endpoint of MRD rate.

For subjects who sign the optional portion of the consent form, an on-study bone marrow biopsy and aspirate will be performed on day 7 which is timed to coincide with expected peak anti-CD19 CAR T cell expansion and tumor infiltration with anti-CD19 CAR T cells following KTE-X19 infusion. Bone marrow biopsies will be analyzed by immunohistochemistry (IHC) to monitor the presence and phenotype of anti-CD19 CAR T cells. IHC will also be used to characterize the tumor microenvironment for tumor and immune related markers. A portion (1 mL) of bone marrow aspirates harvested at subsequent time points, coinciding with standard of care disease assessment, will also be evaluated by flow cytometry for anti-CD19 CAR T cell persistence, phenotype and activity. The presence and status of normal and leukemic $CD19^{+}$ cells will also be monitored by flow cytometry.

Additional exploratory analysis of tumor or immune cell markers that correlate with response to KTE-X19 or disease prognosis will be executed.

These samples and any other components from these samples may be stored up to 15 years to address exploratory research questions related to the treatment or disease under study. Each subject will have the right to have the sample material destroyed at any time by contacting the investigator who in turn can contact the sponsor**.** The investigator should provide the sponsor the study and subject number so that the sample can be located and destroyed.

For subjects who withdraw consent, any samples that were not requested to be returned or destroyed will remain with the sponsor and any data that may be generated will be entered in the study database.

7.11. Procedures by Study Period

Investigative sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected on the screening log should include limited information such as the date of screening, date the subject was enrolled or the reason for why the subject failed screening.

7.11.1. Screening

The screening period begins on the date the subject signs the IRB/IEC approved ICF and continues through enrollment. Informed consent must be obtained before completion of any study specific procedures. Procedures that are part of SOC are not considered study specific procedures and may be performed prior to obtaining consent and used to confirm eligibility. Confirmation of this data must occur within the time allowance as outlined below and in the SOA.

After written informed consent has been obtained, subjects will be screened to confirm study eligibility and participation. Only subjects who meet the eligibility criteria listed in Section 5 and who commence leukapheresis will be enrolled into the study. If at any time prior to enrollment the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure on the subject screening log with the reasons for failing screening.

The following assessments/procedures are to be completed during the screening period at the time points outlined in the SOA:

- Medical history (see Section 7.3)
- Physical examination including height and weight (see Section 7.4)
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- EQ-5D (Phase 2 subjects only; see Section 7.4)
- Neurological assessment (see Section 7.5)
- ECG (see Section 7.6)
- Left ventricular ejection fraction (LVEF) and pericardial effusion assessment (ECHO) (see Section 7.6)
- Labs (see Section 7.8)
  - β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
  - Chemistry panel
  - CBC with differential
  - Peripheral blood
  - CD19 immunophenotyping on peripheral blood or bone marrow aspirate
  - Lumbar puncture for collection of CSF (see Section 7.7)
  - For EU sites, viral serologic tests (eg, HIV, hepatitis B, hepatitis C) will be carried out per institution guidelines and EU regulations. This may be done within the 30 days prior to leukapheresis and/or on the day of leukapheresis.
- CSF prophylaxis if indicated (see Section 6.4)
- Chest x-ray (not required if other imaging modalities are used for baseline assessment of chest)
- Disease assessment (see Section 7.7 and Section 7.9)

- Screening bone marrow evaluation:

  — If available, archival formalin-fixed paraffin embedded (FFPE) bone marrow block and/or slides used for the original diagnosis of ALL will be submitted to the central laboratory

  — A bone marrow aspirate and biopsy is required at screening and will be performed after the last dose of systemic chemotherapy and within approximately 14 days before enrollment to establish baseline disease.

    ■ If there is a delay between when the screening bone marrow is performed and the apheresis, contact the Kite Medical Monitor for guidance on whether or not bone marrow evaluation needs to be repeated. If a fresh bone marrow aspirate and biopsy was recently collected and properly stored prior to consent, then contact the Kite Medical Monitor to confirm if this sample is adequate for screening.

- Serious Adverse Event reporting (refer to Section 9)

- Concomitant medications documentation and previous cancer treatment history (see Section 6.7)

7.11.2. Rescreening

Subjects who are unable to complete or fail to meet the eligibility criteria during the 28-day screening period will be allowed to rescreen. Subjects will retain the same subject indentifcation number assigned at the original screening. If rescreening occurs within 28 days of the signing of the original informed consent, the assessment or procedure that initially resulted in the subject failing screening will be performed, including any other procedures that fell outside of the designated screening window (ie, lab assessments); all other initial screening procedures/assessments do not need to be repeated.

7.11.3. Enrollment/Leukapheresis

Before leukapheresis commences, the following criteria must be met:

- In general, all eligibility criteria confirmed during screening must not be known to be violated prior to leukapheresis. Additionally, the investigator must review and confirm that the last CBC with differential and chemistry panel drawn prior to the start of leukapheresis must meet the eligibility criteria detailed in Inclusion criterion 105. If any screening assessments or procedures are repeated between screening and the start of leukapheresis and results are outside the eligibility criteria (Section 5), contact the Kite medical monitor before proceeding with leukapheresis.

- Subjects must have no evidence of clinically significant infection prior to leukapheresis. Should a subject have clinically significant infection immediately prior to leukapheresis, cell collection must be delayed until the event resolves.

- If leukapheresis is delayed beyond 5 days, a CBC with differential and chemistry panel must be repeated.

- If WBC collected at time of leukapheresis is ≥ 50,000 cells/μL a contact must be made to the Kite Medical Monitor before proceeding with leukapheresis.

- Corticosteroid therapy at a pharmacologic dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis (see Section 6.8).

Once a subject commences leukapheresis, the subject will be considered enrolled into the study.

The following procedures/requirements will occur on the leukapheresis collection day (enrollment) and as outlined in the SOA:

- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature

- Weight (weight must be collected on the day of leukapheresis)

- Labs (to be drawn prior to leukapheresis either on the day of or the day before leukapheresis) (see Section 7.8)

  — Chemistry Panel

  — C-reactive protein; if CRP is ≥ 100 mg/L, contact the Kite Medical Monitor before proceeding with Conditioning chemotherapy

  — CD3 count

  — CBC with differential

  — Anti-KTE-X19 antibody

  — Blood draw for PBMCs and cytokine levels

- Leukapheresis (see Section 6.2)

- Adverse/Serious Adverse Event reporting (refer to Section 9)

- Concomitant medications documentation (see Section 6.7)

Vitals, lab draws, adverse/serious adverse event reporting and concomitant medications documentation may be performed the day before leukapheresis, unless otherwise specified.

7.11.4. Bridging Chemotherapy Period

If prescribed, bridging chemotherapy will be administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy (see Section 6.3).

The following procedures will be performed:

- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- Labs (to be drawn prior to chemotherapy) (see Section 7.8)
  - Chemistry Panel
  - CBC with differential
- Bridging chemotherapy (see Section 6.3)
- Adverse/Serious Adverse Event reporting (refer to Section 9)
- Concomitant medications documentation (see Section 6.7)

Note: As appropriate, vitals and labs should be repeated each day bridging chemotherapy is administered.

7.11.5. CSF Prophylaxis Period

Intrathecal chemotherapy for CSF Prophylaxis will be administered any time during screening through 7 days prior to KTE-X19 infusion (see Section 6.4).

The following procedures will be performed:

- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- Labs (to be drawn prior to chemotherapy) (see Section 7.8)
  - Chemistry Panel
  - CBC with differential
  - Lumbar puncture for collection of CSF (see Section 7.7)
- Intrathecal chemotherapy (see Section 6.4)
- Adverse/Serious Adverse Event reporting (refer to Section 9)
- Concomitant medications documentation (see Section 6.7)

Note: As appropriate, vitals and labs should be repeated each day CSF prophylaxis is administered.

7.11.6. Conditioning Chemotherapy and KTE-X19 Infusion

Administration of KTE-X19 cells to subjects with ongoing infection or inflammation, even if such processes are asymptomatic, increases the risk of high grade and fatal toxicity. All efforts should be made to rule out such conditions prior to cell infusion.

Signs, symptoms or abnormal laboratory results attributed to the malignancy (elevated C-reactive protein [CRP]) are diagnoses of exclusion that require a documented workup to establish. Conditioning chemotherapy and KTE-X19 infusion should only be initiated after it is reasonably assured that cell infusion can safely proceed.

The investigational medicinal product (KTE-X19) must be available before initiation of conditioning chemotherapy.

Refer to Section 7.11.7.5 for Requirements to Work-up Potential Infectious and/or Inflammatory States.

7.11.6.1. Conditioning Chemotherapy Period

7.11.6.1.1. Requirements for Initiating Conditioning Chemotherapy

If any of the following criteria are met prior to the initiation of conditioning chemotherapy, then the work-up listed in Section 7.11.7.5 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38ºC within 72 hours before conditioning chemotherapy
- CRP > 100 mg/L any time between enrolment to start of conditioning chemotherapy
- WBC count or WBC differential concerning for infectious process between enrollment to start of conditioning chemotherapy (eg, WBC > 20,000, rapidly increasing WBC, or differential with high percentage of segments/bands)

Additionally,

- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of conditioning chemotherapy and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with conditioning chemotherapy.
- Complete history and physical exam including HEENT, cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.
- The subject must not have received systemic anti-microbials for the treatment of a known or suspected infection within 48 hours before conditioning chemotherapy (prophylactic use of anti-microbials is allowed).

- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.

- If a subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determined by the investigator in consultation with infectious disease service (if applicable)

- Most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (eg, bacterial, viral serologies, PCR, stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for cultures to become positive.

Once the above criteria are met, then the subject can proceed with conditioning chemotherapy.

7.11.6.2. Conditioning Chemotherapy Administration (Day -4 Through Day -2 Prior to KTE-X19 Infusion)

Subjects will receive a conditioning chemotherapy regimen consisting of cyclophosphamide and fludarabine. The first dose of conditioning chemotherapy will be designated as Day –4. Subjects will initiate conditioning chemotherapy with cyclophosphamide and fludarabine beginning on Day –4 and through Day –2, with 1 rest day (Day -1) before receiving KTE-X19. The 3-day conditioning chemotherapy regimen will be administered in an outpatient setting.

Conditioning chemotherapy (fludarabine and cyclophosphamide) will be supplied by the investigative site unless otherwise noted and should be administered per institutional guidelines. Refer to the current product label for guidance on packaging, storage, preparation, administration and toxicity management associated with the administration of chemotherapy agents.

Before conditioning chemotherapy commences, the criteria outlined in Section 7.11.6.1 must be met.

Provided the criteria for conditioning chemotherapy are met, the 3-day conditioning regimen of fludarabine and cyclophosphamide will be administered in accordance with the following daily dosing instructions:

- Subjects should receive IV hydration with conditioning chemotherapy per institutional guidelines or investigator discretion; recommendations for IV hydration are listed below:

- IV pre-hydration starting 90 minutes prior to fludarabine and continuing for at least 8 hours after with 0.45% sodium chloride and 5% dextrose (or other composition appropriate for the clinical situation) at a rate of at least 90 mL/m^2/hour. Hydration may be temporarily interrupted to give fludarabine or cyclophosphamide but should continue until at least 8 hours after the cyclophosphamide dose has been completed.

- Fludarabine 25 mg/m^2/day IV in 50 mL of 0.9% sodium chloride over 30 minutes on Day -4, Day -3, Day -2 followed by:

- Cyclophosphamide at a dose of 900 mg/m^2/day IV over 60 minutes on Day -2 only
- Add mesna per institutional guidelines
- Subjects should be instructed to drink plenty of liquids during and for 24 hours following the chemotherapy (total fluids approximately 1.5 L/m^2/24 hours IV + PO). In general, subjects should be kept well hydrated but closely monitored to prevent fluid overload.
- Subjects should be instructed to drink plenty of liquids during and for 24 hours following the chemotherapy (approximately 2 liters/24 hours) if no contraindications. In general subjects should be kept well hydrated but closely monitored to prevent fluid overload.

7.11.6.3. Conditioning Chemotherapy Procedures

The following procedures will be completed during Day -4 to Day -2. Day -1 is a rest day.

- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- Labs (to be drawn prior to chemotherapy) (see Section 7.8)
  - β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
  - Chemistry Panel
  - CBC with differential
    - Note: If subject did not have bridging therapy and hence bone marrow is not collected between the end of bridging chemotherapy and start of Conditioning chemotherapy, then sites must assess peripheral blasts counts during this time period (eg, at Day -4).
  - Blood draw for PBMCs and cytokine levels
- Bone marrow evaluation (see Section 7.9.1)
  - In subjects who receive bridging chemotherapy, an additional bone marrow sample is required between the end of bridging chemotherapy and Day -4. If bridging chemotherapy is not administered, then the additional bone marrow sample is not required.
- Conditioning chemotherapy (Fludarabine and cyclophosphamide) administration (see Section 6.5)
- Adverse/Serious Adverse Event reporting (refer to Section 9)
- Concomitant medications documentation (see Section 6.7)

7.11.7. Investigational Product Treatment Period

7.11.7.1. Pre-KTE-X19 Infusion Criteria

If any of the following criteria are met prior to the initiation of KTE-X19, then the work-up listed in Section 7.11.7.5 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°C within 72 hours of KTE-X19 infusion
- CRP > 100 mg/L any time between enrollment to start of KTE-X19 infusion
- WBC count or WBC differential concerning for infectious process between enrollment to start of KTE-X19infusion (eg, WBC > 20,000, rapidly increasing WBC, or differential with high percentage of segments/bands)

Additionally:

- All eligibility criteria of the protocol must be met. If any screening assessments or procedures are repeated between confirmation of eligibility and the start of KTE-X19 infusion and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with KTE-X19 infusion (except for peripheral blood cell counts that have been impacted by conditioning chemotherapy).
- Complete history and physical exam including HEENT, and cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.
- The subject must not have received systemic anti-microbials for the treatment of a known or suspected infection within 48 hours before KTE-X19 (prophylactic use of anti-microbials is allowed).
- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.
- If a subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determined by the investigator in consultation with infectious disease service (if applicable).
- Most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (eg, bacterial, viral serologies, PCR, stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for cultures to become positive.

Once the above criteria are met, then the subject can proceed with administration of KTE-X19.

If the KTE-X19 infusion is delayed > 2 weeks, protocol guidelines should be followed regarding the need for repeat conditioning chemotherapy.

7.11.7.2. Hospitalization for KTE-X19 Infusion

Subjects will be hospitalized to receive infusion of KTE-X19 followed by a minimum 7 day observation period unless otherwise required by country regulatory agencies (refer to Appendix 3 for details).

Subjects will remain in the hospital through day 7 post infusion of KTE-X19. Subjects should not be discharged from the hospital until all KTE-X19-related non-hematological toxicities return to grade ≤ 1 or return to baseline. Subjects may be discharged with non-critical and clinically stable or slowly improving toxicities (eg, renal insufficiency) even if > grade 1, if deemed appropriate by the investigator. Subjects should remain hospitalized for ongoing KTE-X19-related fever, hypotension, hypoxia, or ongoing central neurological toxicity > grade 1, or if deemed necessary by the treating investigator.

Given the possibility that a subject could develop CRS or neurologic events in the outpatient setting after discharge, subjects and their family members/caregivers should be educated on potential symptoms of these syndromes such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. If subjects develop these symptoms, they should be instructed to immediately contact the principal investigator or seek immediate medical attention.

See Section 6.8 for excluded medications prior to and after KTE-X19.

7.11.7.3. KTE-X19 Premedication Dosing

The following pre-KTE-X19 infusion medications should be administered approximately 1 hour prior to infusion. Alternatives to the recommendations below should be discussed with the Kite medical monitor

- Acetaminophen 650 mg PO or equivalent
- Diphenhydramine 12.5 mg administered either orally or via IV or equivalent

7.11.7.4. KTE-X19 Infusion (Day 0)

Central venous access, such as a port or a peripherally inserted central catheter, is required for the administration of KTE-X19. Catheter care, per institutional guidelines, should be followed. Materials and instructions for the thawing, timing, and administering of KTE-X19 are outlined in the IPM. It is recommended that vital signs are recorded before KTE-X19 infusion and then routinely as clinically indicated (eg, fever ≥ 38.3°C).

The IPM must be reviewed prior to administration of KTE-X19.

Research sites should follow institutional guidelines for the infusion of cell products.

During this period, the following procedures will be completed at the time points outlined in the SOA:

- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature every Q4-6 hours during hospitalization (see Section 7.4 for vital sign requirements during the initial hospitalization)
- ECOG performance status
- EQ-5D (Phase 2 subjects only; see Section 7.4)
- Neurological assessment (see Section 7.5)
- Labs (before KTE-X19 infusion) (see Section 7.8)
  - Chemistry Panel
  - CBC with differential
  - Blood draw for PBMCs and cytokine levels (See SOA for frequency)
  - Recommended: Monitoring of CRP, ferritin, and LDH (only if LDH is elevated at baseline) levels may assist with the diagnosis and define the clinical course in regards to CRS/neurologic events. It is, therefore, recommended that CRP, ferritin, and LDH (if elevated at baseline) be monitored daily starting at Day 0 and continuing through hospitalization. In addition, lactate should be monitored as clinically indicated.
- Lumbar puncture for subjects with first onset grade ≥ 2 neurologic symptoms should be completed for examination of CSF (see Section 7.7)
- As applicable, an additional cytokine sample should be drawn at the first onset and first reoccurrence of any ≥ grade 2 CRS (per Lee 2014 criteria; Table 15) if not already collected on that day
- Bone marrow evaluation (see Section 7.9)
  - For subjects who sign the optional consent form, an additional bone marrow biopsy/aspirate will be collected day 7 post KTE-X19 infusion. If sample cannot be collected on day 7, then sample can be collected between day 7 – 14.
- KTE-X19 pre-medications (see Section 7.11.7.3)
- Infusion of KTE-X19
- Adverse/Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation (see Section 6.7)

7.11.7.5. Requirements to Work-Up Potential Infectious and/or Inflammatory States Prior to KTE-X19 Infusion

In the absence of an identified source of infection (eg, line infection, pneumonia on chest x-ray), the minimum workup to be performed prior to administration of conditioning chemotherapy and/or KTE-X19 consists of:

- Call Kite medical monitor
- Infectious disease service consult (if applicable)
- CT imaging of the chest, abdomen, and pelvis with IV contrast. If there is a medical contraindication to contrast, then non-contrast CT is allowed.
- The following must be performed (prior to the initiation of anti-microbials if clinically feasible):
  - Blood cultures (aerobic and anaerobic x2 bottles each) and UA and urine culture. Deep/induced sputum culture if clinically indicated.
  - All indwelling lines, such as central venous catheters, should be examined for any signs of infection, and additional cultures should be drawn from the line.
  - Nasopharyngeal-throat (NPT) swab or equivalent assay for viral infection such as influenza A/B (including H1N1), parainfluenza 1/2/3, adenovirus, respiratory syncytial virus, coronavirus, metapneumovirus
  - Collection of fungal cultures and markers as appropriate (eg, galactomannan, fungitell)
  - Collection of appropriate serum viral studies (eg, cytomegalovirus [CMV])
- If a central nervous system process is suspected, appropriate brain imaging and subsequent lumbar puncture with cytology, culture, Gram stain, and viral PCR should be performed.
- Any additional sign or symptom-directed investigation should be performed as clinically indicated.

Prior to proceeding with conditioning chemotherapy and/or KTE-X19 infusion, the above workup must not suggest the presence of an active infection, and all requirements for conditioning chemotherapy and/or KTE-X19 infusion must be satisfied. If the KTE-X19 infusion is delayed > 2 weeks following conditioning chemotherapy, protocol guidelines should be followed regarding the need for repeat conditioning chemotherapy.

- If the above workup was triggered due to CRP > 100 mg/L, CRP should be repeated, and if CRP continues to increase significantly, evaluation should be performed for any other potential infectious or inflammatory condition not previously evaluated.

7.11.8. Post-treatment Assessment Period

After completing KTE-X19 infusion and discharged from the hospital, all subjects will be followed in the post treatment assessment period. Counting from day 0 (KTE-X19 infusion), subjects will return to the clinic at the following intervals.

- Day 14 (± 2 days)
- Day 28 (+ 3 days)
- Week 8 (± 1 week)
- Month 3 (± 2 weeks)

Subject will allow key sponsor contacts to continue to access medical records so that information related to subjects health condition and initial treatment response may be obtained.

The following procedures will be completed for subjects as outlined in the SOA:

- Physical exam
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- EQ-5D (Phase 2 subjects only; see Section 7.4)
- Neurological assessment (see Section 7.5)
- Labs (see Section 7.8)
  - β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
  - Chemistry Panel
  - CBC with differential
  - Anti-KTE-X19 antibodies
  - Blood draw for PBMCs and cytokine levels
- Lumbar puncture for subjects with first onset grade ≥ 2 neurologic symptoms should be completed for examination of CSF (see Section 7.7)
- As applicable, an additional cytokine sample should be drawn at the first onset and first reoccurrence of any ≥ grade 2 CRS (per Lee 2014 criteria; Table 15) if not already collected on that day
- Disease Assessment (see Section 7.7 and Section 7.9)

- Adverse/Serious Adverse Event reporting (refer to Section 9)
- Concomitant medications documentation (see Section 6.7)

Following the initial hospitalization for the KTE-X19 infusion, if the subject is hospitalized with any KTE-X19 related adverse event, the following labs will be collected:

- PBMCs on day of admission, then weekly, and on day of discharge
- Cytokine levels on day of admission, then weekly, and on day of discharge

If a subject progresses before completion of the Month 3 visit, then the following procedures will be completed:

- Labs (if not already collected at visit in which progressive disease/relapse was confirmed):
  - Blood draw for PBMC
    - A PBMC sample should be collected at time of progression and prior to starting subsequent anticancer therapy
  - Anti-KTE-X19 antibodies
  - β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
- Proceed to the long term follow-up period (see Section 7.11.9 for details).

7.11.9. Long-term Follow-up Period

All enrolled subjects will be followed in the long term follow-up period for safety, survival and disease status, if applicable. Subjects will begin the long term follow-up period after they have completed the Month 3 visit of the post-treatment assessment period (whether they responded to treatment or went straight to the month 3 visit due to disease progression). After completion of the Month 24 visit, subjects who received an infusion of KTE-X19 will be provided the opportunity to transition to a separate LTFU study, KT-US-982-5968 (refer to section 3.5.3).

- Every 3 months (± 2 weeks) through Month 18
- Every 6 months (± 1 month) between Month 24 - Month 60
- Beginning with year 6, Month 72 (± 3 months), subjects will return to the clinic 1 time annually up to 15 years after the last subject receives their KTE-X19 infusion.

The following procedures will be completed for subjects who are enrolled and receive KTE-X19, at the time points outlined in the SOA:

- Physical exam

- EQ-5D (Phase 2 subjects only; see Section 7.4)
- Disease assessment (see Section 7.7 and Section 7.9)
  - Note: Disease assessment is performed per the SOA through month 24 or until disease progression, whichever occurs first. If the subject's disease has not progressed by Month 24, then after Month 24 disease assessments will be performed per standard of care.
- Survival Status – subjects may be contacted by telephone to confirm survival status
- Labs (see Section 7.8)
  - CBC with differential
  - Anti-KTE-X19 antibodies
    - For serum samples that demonstrate increased anti-KTE-X19 antibodies at the month 3 visit over baseline values, attempts should be made to obtain and test additional serum samples approximately every 3 months until the antibody levels return to baseline (or becomes negative) or up to 1 year from the completion of treatment, whichever occurs first
  - Blood draw for PBMCs
    - A PBMC sample should be collected at time of progression and prior to starting subsequent anticancer therapy
- Targeted Adverse/Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Targeted Concomitant medication documentation (see Section 6.7)
- Subsequent therapy for the treatment of ALL (see Section 6.8)

Subjects who undergo an allogeneic SCT will continue to be followed in the LTFU period and undergo the following assessments at the timepoints outlined in the SOA:

- Disease status
- Survival status
- Serious Adverse Event reporting (see Section 9.4)
- Concomitant medications documentation (see Section 6.7)
- Subsequent therapy for ALL (see Section 6.9)

- Blood draw for:
  - PBMCs
  - If applicable anti-KTE-X19 antibodies (see Section 7.11.9)

Subjects who receive infusion of KTE-X19, but who experience disease progression, will be followed in the LTFU period and undergo the following assessments at the timepoints outlined in the SOA:

- Survival status
- Serious Adverse Event reporting (see Section 9)
- Concomitant medications documentation (see Section 6.7)
- Subsequent therapy for ALL (see Section 6.9)
- Blood draw for:
  - PBMC's
  - If applicable anti-KTE-X19 antibodies (see Section 7.11.9).

Subjects who are enrolled/leukapheresed, but did not receive KTE-X19 treatment, will be followed and will undergo the following assessments at the timepoints outlined in the SOA only until the end of this study (refer to Section 3.5.2):

- Disease assessment per standard of care
- Survival status
- Subsequent therapy for the treatment of ALL (see Section 6.9)
- Adverse/Serious Adverse Event reporting (refer to Section 9)
- Concurrent therapies (see Section 6.7)

Should the subject fail to return to the clinic for a scheduled protocol-specific visit, sites will need to make 2 attempts by a combination of telephone and mail to contact the subject. Sites must document both attempts to contact the subject. If a subject does not respond within 1 month after the second contact the subject will be considered lost to follow-up and no additional contact will be required.

Table 4. Schedule of Assessments

Schedule of Assessments (1 of 2) Procedures	Screening [9]	Enrollment / Leukapheresis	Bridging Chemotherapy	CSF Prophylaxis	Conditioning Chemotherapy Period				IP Administration Period [11]		Post Treatment Follow-up [10, 11] (each visit calculated from Day 0)			
Visit Frequency	**≤ 14 days before enrollment**	**≤ ~5 days after eligibility confirmation**	**Bridging Chemotherapy**	**CSF Prophylaxis**	**-4**	**-3**	**-2**	**-1**	**0**	**1 – 7 [13]**	**Day 14 (± 2 days)**	**Day 28 (+ 3 days)**	**Week 8 (± 1 week)**	**Month 3 (± 2 weeks)**
Medical history	X													
Physical exam	X										X	X	X	X
Vital signs [1]	X [1]	X [5]	X [7]	X [7]	X	X	X		X [1]	X [1]	X	X	X	X
Weight	X	X [5]												
ECOG Performance Status	X				X				X					
Neurological Assessment [8]	X								X	X [8]		X		X
EQ-5D (Phase 2 subjects only) [14]	X								**X**			X		X
ECG	X[9]													
LVEF and PE assessment by ECHO	X[9]													
Chest x-ray	X													
Bone Marrow Evaluation (biopsy and aspirate) for Disease Assessment [2]	X [2]				X [2]					Opt. Day 7 Bx & A [2]		X [2]	X [2]	X [2]
Extramedullary Imaging [3]	X [3]											X [3]	X [3]	X [3]
Overall Response Assessment (Appendix 1)												X	X	X
Leukapheresis [5]		X												
CSF Prophylaxis [6]	X [6]													
Bridging Chemotherapy [6]		X [6]												
Conditioning Chemotherapy (Fludarabine & Cyclophosphamide) [6]					X	X	X							

Schedule of Assessments (1 of 2) Procedures	Screening [9]	Enrollment / Leukapheresis			Conditioning Chemotherapy Period				IP Administration Period [11]		Post Treatment Follow-up [10, 11] (each visit calculated from Day 0)			
Visit Frequency	≤ 14 days before enrollment	≤ ~5 days after eligibility confirmation	Bridging Chemotherapy	CSF Prophylaxis	-4	-3	-2	-1	0	1 – 7 [13]	Day 14 (± 2 days)	Day 28 (+ 3 days)	Week 8 (± 1 week)	Month 3 (± 2 weeks)
KTE-X19 infusion IV									X[12]					
Pregnancy test (serum or urine β-HCG)	X				X									X
Chemistry panel & CBC with differential [7]	X	X [5]	X [7]	X [7]	X	X	X		X	X	X	X	X	X
CD3 count		X [5]												
CD19 immunophenotyping	X [9]													
C-Reactive Protein		X [5]												
Lumbar Puncture for collection of CSF[4]	X [4]			X [4]					X [4]			X [4]		
Anti-KTE-X19 antibody		X [5]										X		X
Peripheral blood	X [7]			X [7]										
Blood draw for PBMCs [11]		X [5]			X [6]					Day 7	X	X	X	X
Blood draw for cytokines [11]		X [5]			X [6]				X	Day 3 and 7	X	X		
Adverse events/ Concomitant medication	X	→												

Footnotes for Schedule of Assessments (1 of 2)

1 Vital signs: Includes blood pressure, heart rate, oxygen saturation, and temperature. Height will be collected at screening. Vitals will be monitored before and after the KTE-X19 infusion and then routinely (every 4-6 hours) while hospitalized. If the subject has a fever (temperature 38.3oC or greater) at any time during hospitalization, vital signs will be monitored more frequently as clinically indicated.

2 Bone Marrow Evaluation (biopsy and aspirate) for Disease Assessment (Section 7.9): For screening bone marrow evaluation see section 7.9.1. A bone marrow aspirate will be required at all timepoints per the SOA table above (Subjects that receive an SCT, bone marrow evaluations are not required for the first 100 days post SCT). In addition to the bone marrow aspirate, a bone marrow biopsy is required at Screening, Day -4 and Day 28. The Day -4 bone marrow biopsy is only required for subjects receiving bridging chemotherapy. A bone marrow biopsy at all other timepoints is recommended and should be performed if standard of care. Anytime the bone marrow aspirate is a dry tap, then a bone marrow biopsy is required. Disease status will be evaluated per institutional practices. A portion of the aspirate collected will be submitted to the central lab on the day of collection and analyzed for MRD; see the central laboratory manual for details. The optional day 7 bone marrow biopsy and aspirate may be performed between day 7 and 14. Overall response will be assessed by the investigator per Appendix 1. If bone marrow blasts are ≤ 5% and circulating blasts are ≥ 1%, then additional studies (eg, flow cytometry) should be performed to quantify the blasts.

3 Extramedullary Imaging (Section 7.9.2): For subjects with known baseline extramedullary disease detected through imaging, baseline images appropriate for the anatomical location and clinical scenario will be performed. For subjects receiving bridging chemotherapy, images will be performed after bridging chemotherapy and before conditioning chemotherapy. For subjects not receiving bridging chemotherapy, images will be performed within 28 days before conditioning chemotherapy. On study images will be performed with the same imaging modality and anatomical location as imaged at baseline. Following KTE-X19 infusion, the first on study images will occur at the first occurrence of leukemia remission based on the bone marrow evaluation. Subsequent images will continue as per the SOA through Month 24 or disease progression, whichever occurs first. If the subject's disease has not progressed by Month 24, then images will be performed per standard of care until disease progression. For subjects with or without extramedullary disease, images should be performed per standard of care anytime the subject presents with symptoms suggestive of disease progression.

4 Lumbar Puncture (Section 7.7): CSF samples will be analyzed locally for disease assessment and centrally for disease assessment and toxicity evaluation at the following timepoints: 1) Baseline – a CSF result obtained within 30 days before enrollment will be acceptable eligibility determination, 2) at the time of CSF prophylaxis, 3) for subjects with baseline CNS-2 disease, a CSF sample is required at the time of first presumed response based on bone marrow (bone marrow <5%), 4) first onset of grade 2 or greater neurological symptoms or as medically indicated 5) for subjects with a CR, collection and analysis of CSF is required to confirm CR and 6) per institutional standard of care. Should a subject have an Ommaya reservoir and there is no evidence of blockage of CSF flow from the spinal canal, withdrawal of the CSF sample though the reservoir is acceptable. CSF samples (ie, collected on or after informed consent) will be submitted to the central laboratory.

5 Leukapheresis (Sections 6.2 and 7.11.3): All leukapheresis criteria must be met before leukapheresis commences. Vitals, weight, and laboratory sample draws may be performed the s day of or before leukapheresis, except weight must be collected on day of leukapheresis. All laboratory samples should be drawn before the leukapheresis procedure. For EU sites, viral serologic tests (eg, HIV, Hep B, Hep C) will be carried out per institution guidelines and EU regulations. This may be done within the 30 days prior to leukapheresis and/or on the day of leukapheresis (see Section 7.11.1).

6 Chemotherapies: Bridging chemotherapy (Section 6.3) will be administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy. CSF prophylaxis (Section 6.4) will be administered any time during screening through 7 days before the KTE-X19 infusion. Subjects who are enrolled with CNS-2 disease at baseline must receive CSF prophylaxis after leukapheresis and at least 7 days prior to KTE-X19, unless otherwise approved by the Kite Medical Monitor. Multiple doses of CSF prophylaxis can be given per investigator discretion in accordance with institutional guidelines, but at least 7 days must pass between the last dose of CSF prophylaxis and KTE-X19. Should a subject have an Ommaya reservoir and there is no evidence of blockage of CSF flow from the spinal canal, administration of CSF prophylaxis through the reservoir is acceptable. Conditioning chemotherapy (Section 6.5) consisting of fludarabine on Day -4, -3, -2 prior to KTE-X19 and cyclophosphamide on Day -2 prior to KTE-X19 will be administered.

7 Vitals, Chem panel, and CBC: collected each day prior to CSF prophylaxis and bridging chemotherapy (see Section 7.11.4 and 7.11.5). CBC 5-part preferred, but 3-part will be acceptable. Peripheral blood: Peripheral blood will be collected at screening, and if the subject did not have bridging therapy than peripheral blood will be collected during day -4 and submitted to the central lab.

8 Neurological assessment: Subjects neurological status should be evaluated at screening to establish a baseline. After enrollment, subjects should be evaluated for any neurological symptoms at each of the timepoints specified in the SOA. During the hospitalization period, evaluations of neurological status may need to be increased.

9 Screening procedures (Section 7.11.1): Procedures should be performed within 14 days of enrollment (unless otherwise specified). ECG: must be performed within 30 days prior to enrollment; ECHO: If the last chemotherapy regimen the subject received is not considered cardiotoxic, then an ECHO performed within 28 days prior to signing the consent may be used for eligibility. If the last chemotherapy regimen the subject received is considered cardiotoxic, then an ECHO performed following the subjects last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility. CD19: Local CD19 immunophenotyping will be performed at screening on peripheral blood or bone marrow aspirate. Surface CD19 expression should be measured by flow cytometry; IHC analysis is allowed if the bone marrow aspirate is a dry tap, inadequate or there were insufficient circulating blasts for flow cytometry. Procedures that are part of SOC are not considered study specific procedures and may be performed prior to obtaining consent and used to confirm eligibility provided they are performed within the time allowance as outlined in the SOA.

10 If the subject progressions before Month 3: Refer to section 7.11.8 for the procedures that are to be completed.

11 Following the initial hospitalization for the KTE-X19 infusion (Section 7.11.8): Following the initial hospitalization for the KTE-X19 infusion, if the subject is hospitalized with any KTE-X19 related adverse event, a blood sample for PBMCs and cytokines will be collected on day of admission, then weekly, and on day of discharge. A PBMC sample should be collected at time of progression and prior to starting subsequent anticancer therapy. As applicable, an additional cytokine sample should be drawn at the first onset and first reoccurrence of any > grade 2 CRS (per Lee 2014 criteria) if not already collected on that day.

12 KTE-X19 pre-medications: Subjects will receive acetaminophen and diphenhydramine (equivalent) approximately 1 hour prior to KTE-X19 (see Section 7.11.7.3).

13 Please refer to Appendix 3 for requirements by country regulatory agencies

14 EQ-5D: The EQ-5D will be completed prior to other study related procedures or assessments.

Schedule of Assessments (2 of 2) Procedures	**Long Term Follow-up Period [8, 9] (Each visit calculated from Day 0)**												
Visit Frequency	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 24**	**Month 30**	**Month 36**	**Month 42**	**Month 48**	**Month 54**	**Month 60**	**Month 72 and Annually Up to 15 Years**
Physical exam	X	X	X	X	X	X							
EQ-5D (Phase 2 subjects only)	**X**	**X**	**X**	**X**	**X**	**X**							
Bone Marrow Evaluation (biopsy and aspirate) for Disease assessment [1]	X	X	X	X	X	X							
Extramedullary Imaging [2]	X [2]	X [2]	X [2]	X [2]	X [2]	X [2]							
Overall Response Assessment (Appendix 1)	X	X	X	X	X	X							
Survival Status [4, 7, 8]	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with differential (5 part preferred, 3 part acceptable)	X	X	X	X	X	X							
Anti-KTE-X19 antibody [3, 8]													
Blood draw for PBMCs [8]	X	X	X	X	X	X		X		X		X	X
Adverse Event Reporting [4]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications Reporting [5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Subsequent therapy for ALL [6, 8]	X	X	X	X	X	X	X	X	X	X	X	X	X

1 Bone Marrow Evaluation (biopsy and aspirate) for Disease Assessment (Section 7.9.1): A bone marrow biopsy and aspirate will be performed per the SOA through Month 24 or until disease progression, whichever occurs first. Disease status will be evaluated per institutional practices. The slides used for the local evaluation of % blasts should be submitted to the central laboratory along with the corresponding pathology report. If the subject's disease has not progressed by Month 24, then after Month 24 bone marrow evaluation will be performed per SOC.

2 Extramedullary Imaging (Section 7.9.2): For subjects with baseline extramedullary disease: Following KTE-X19 infusion, the first on study images will occur at the first occurrence of leukemia remission based on the bone marrow evaluation. Subsequent images will continue as per the SOA through Month 24 or disease progression, whichever occurs first. If the subject's disease has not progressed by Month 24, then images will be performed per standard of care until disease progression. For subjects with or without extramedullary disease, images should be performed per SOC anytime the subject presents with symptoms suggestive of disease progression.

3 Anti-KTE-X19: For antibody sample collection in long-term follow-up, refer to Section 7.11.9 for details.

4 AE/SAE reporting (Sections 9.2 and 9.4): AEs: After 3 months, only targeted adverse events will be reported in the CRF through 24 months after KTE-X19 infusion or disease progression, whichever occurs first. SAEs: After 3 months, only targeted serious adverse events (including targeted grade 5 serious adverse events) will be reported through 24 months after KTE-X19 infusion or disease progression, whichever occurs first, within 24 hours using the SAE Report Form and in the CRF. Targeted adverse events include central neurological, hematological, infections, GVHD, autoimmune disorders, and secondary malignancies. Subjects who receive an allogeneic SCT will only be followed for KTE-X19 related serious adverse events. Reporting of these SAEs will commence at the time the SCT preparative regimen commences through 24 months after KTE-X19 infusion or disease progression, whichever occurs first, within 24 hours using the SAE Report Form and in the CRF. In addition to the above SAE reporting requirements, anytime a KTE-X19 related serious adverse event occurs it will be reported within 24 hours using the SAE Report Form and in the CRF. All deaths that occur from ICF through end of study will be reported in the CRF.

5 Concomitant medications reporting (Section 6.7): After 3 months of follow-up, only targeted concomitant medications will be collected for 24 months after KTE-X19 infusion or disease progression, whichever occurs first. Targeted concomitant medications include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations.
6 Subsequent therapy for ALL (Section 6.9): Documentation of subsequent therapy for ALL will continue to be documented while the subject remains on study. Subjects may be contacted by telephone.
7 Survival Status (Section 7.11.9): Subjects may be contacted by telephone to confirm survival status.
8 If the subject progresses in the LTFU phase (Section 7.11.9), the subject will be followed in the LTFU phase for survival status, subsequent therapy for ALL and have blood drawn for PBMC's and if applicable anti-KTE-X19 antibodies. A PBMC sample should be collected at the time of progression and prior to starting subsequent anticancer therapy.
9 After completion of at least 24 months of assessments in the KTE-C19-103 study, subjects who received an infusion of KTE-X19 will be provided an opportunity to transition to the LTFU study (KT-US-982-5968) after providing signed informed consent, to complete the remainder of the 15-year LTFU period.

8. SUBJECT WITHDRAWAL

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue to receive study required treatment and/or other protocol required procedures at any time during the study but continue to participate in the study. This is referred to as partial withdrawal of consent.

If partial withdrawal of consent occurs, the investigator must discuss with the subject the appropriate process for discontinuation from investigational product, study treatment or other protocol required therapies and must discuss options for continued participation, completion of procedures and the associated data collection as outlined in the SOA. The level of follow-up and method of communication should also be discussed between the research staff and the subject and documented in the source documents.

Withdraw of full consent for a study means that the subject does not wish to receive further protocol required therapy or undergo procedures and the subject does not wish to continue further study follow-up. Subject data collected up to withdraw of consent will be retained and included in the analysis of the study, and where permitted by local regulations, publically available data (death records) can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

As part of the study sites may be asked to conduct searches of public records, such as those establishing survival status, if available, to obtain survival data for any subject for whom the survival status is not known. Sites may be also asked to also retrieve autopsy reports to confirm status of disease at the time of death.

The investigator and/or sponsor can also decide to withdraw a subject from the investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole or at any time prior to study completion.

8.1. Reasons for Removal from Treatment

Reasons for removal from protocol required investigational products or procedures include any of the following:

- Adverse Event
- Subject request
- Product not available
- Lost to Follow-up
- Death
- Decision by sponsor

8.2. Reasons for Removal from Study

Reasons for removal of a subject from the study are as follows:

- Subject withdrawal of consent from further follow-up
- Investigator decision
- Lost to follow-up
- Death

9. SAFETY REPORTING

9.1. Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. When recording such events, provide descriptions that the pre-existing condition has changed (eg, more frequent headaches for a subject with pre-existing headaches or blood pressure is now more increased in a subject with pre-existing hypertension). A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

Interventions for pretreatment conditions (such as elective cosmetic surgery) or medical procedures that were planned before study participation are not considered adverse events. Hospitalization for study treatment infusions or precautionary measures per institutional policy are not considered adverse events.

The term "disease progression" or any relapse after a remission should not be reported as adverse events. Death due to disease progression in the absence of signs and symptoms of underlying disease should be reported as the primary tumor type (eg, B-cell type acute leukemia).

For situations when an adverse event or serious adverse event is due to the disease under investigation report the signs and symptoms. Worsening of signs and symptoms of the malignancy under study should also be reported as adverse events in the appropriate section of the CRF.

The investigators clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject requests to withdraw from protocol required therapies or the study due to an adverse event, the subject should undergo the procedures outlined in the Month 3 visit of the SOA.

9.1.1. Diagnosis Versus Signs and Symptoms

For adverse events, a diagnosis (if known) rather than individual signs and symptoms should be recorded on the AE form. The exception is for CRS where both the diagnosis and signs and symptoms will be captured on the CRF AE form. For signs and symptoms of the underlying cancer, the signs and symptoms should be captured. However, on the AE form, the investigator should state that these signs and symptoms are due to the underlying disease.

9.1.2. Abnormal Vital Sign Values

Not all vital sign abnormalities qualify as an adverse event. A vital sign result must be reported as an adverse event if it is a change from baseline and meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding if an isolated vital sign abnormality should be classified as an adverse event. However, if a clinically significant vital sign abnormality is a sign of a disease or syndrome (eg, high blood pressure), only the diagnosis (ie, hypertension) should be recorded on the CRF.

9.1.3. Reporting Abnormal Laboratory Findings

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as AEs. However, abnormal laboratory findings that result in new or worsening clinical sequelae or that require therapy or adjustment in current therapy, are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

An abnormal laboratory test result must be reported as an adverse event if it is a change from baseline and meets any of the following criteria:

- Associated with clinical symptoms
- Results in a medical intervention (eg, potassium supplementation for hypokalemia or iron replacement therapy for anemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

9.2. Reporting of Adverse Events

The investigator is responsible for reporting all AEs observed by the investigator or reported by the subject as follows in Table 5:

Table 5. Reporting Requirements for Adverse Events

Subjects who are enrolled, but do not receive KTE-X19 infusion	Subjects who are enrolled and receive KTE-X19 infusion
• Adverse events that occur from enrollment (ie, commencement of leukapheresis) through 30 days after the last study specific procedure (eg, leukapheresis, bridging chemotherapy, conditioning chemotherapy) or until initiation of a new anti-cancer therapy, whichever occurs first, will be reported	• AEs that occur from enrollment (ie, commencement of leukapheresis through 3 months after treatment with KTE-X19 infusion will be reported • After 3 months, only targeted AEs will be reported through 24 months after KTE-X19 infusion or disease progression, whichever occurs first, will be reported ○ Targeted adverse events include central neurological events, hematological events, infections, GVHD, autoimmune disorders, and secondary malignancies. • Subjects who receive an allogeneic SCT will only be followed for KTE-X19-related SAEs.

Abbreviations: GVHD, graft-versus-host-disease.
See Section 9.5 for reporting requirements.
See Section 6.7 for targeted concomitant medications and Section 9.5 for targeted SAEs reporting requirements.
See Section 9.5 for reporting requirement for non-serious CRS events Grade ≥ 3.

The investigator must address the below AEs:

- Adverse event diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to investigational product, chemotherapy or study procedures
- Action taken

Adverse event grading scale used will be the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. A copy of the grading scale can be downloaded from the CTEP home page (http://ctep.cancer.gov). Cytokine Release Syndrome events will also be reported using the grading scale outlined in the KTE-X19 IB.

In reviewing adverse events, investigators must assess whether the adverse event is possibly related to 1) leukapheresis, 2) bridging chemotherapy, 3) CSF prophylaxis, 4) Conditioning chemotherapy, 5) the investigational product (KTE-X19), or any protocol required study procedure. The relationship is indicated by a yes or no response and entered into the CRF. A yes response should indicate that there is evidence to suggest a causal relationship between the study treatment or procedure and the adverse event. Additional relevant data with respect to describing the adverse event will be collected in the CRFs.

The investigator is expected to follow reported adverse events until stabilization or resolution. If a subject begins a new anti-cancer therapy, the AE reporting period for non-SAEs ends at the time the new treatment is started.

9.3. Definition of Serious Adverse Events

A SAE is defined as an AE that meets at least 1 of the following serious criteria:

- Fatal
- Life threatening (places the subject at immediate risk of death)
- Requires in patient hospitalization or prolongation of existing hospitalization
  - An AE would meet the criterion of "requires hospitalization" if the event necessitated an admission to a healthcare facility (eg, overnight stay).
  - Events that require an escalation of care when the subject is already hospitalized should be recorded as an SAE. Examples of such events include movement from routine care in the hospital to the intensive care unit (ICU) or if that event resulted in a prolongation of the existing planned hospitalization.
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event
  - If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as an SAE with the criterion of "other medically important serious event."
- The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event according to NCI CTCAE criteria; the event itself may be of relatively minor medical significance and, therefore, may not meet the seriousness criteria. Severity and seriousness need to be independently assessed for each adverse event recorded on the CRF.
- Progression of the malignancy during the study should not be reported as a AE. However, signs and symptoms of disease progression may be recorded as AEs or SAEs and indicated as being due to disease progression in the CRF. If the malignancy has a fatal outcome before the end of the SAE reporting period, the event leading to the death must be recorded as an SAE with the outcome of being fatal.

9.3.1. Hospitalization and Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE as described in Section 9.5.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for palliative care or hospice care
- Planned hospitalization required by the protocol (eg, for monitoring of the subject or to perform an efficacy measurement for the study)
- Planned hospitalization for a pre-existing condition
- Hospitalization due to progression of the underlying cancer

9.4. Reporting Deaths

Death must be reported if it occurs during the SAE reporting period, irrespective of any intervening treatment.

Any death occurring after the first dose of chemotherapy, for the purpose of pre-conditioning, and within 3 months of KTE-X19 infusion, regardless of attribution to treatment, requires expedited reporting within 24 hours. Any death occurring after the SAE reporting period requires expedited reporting within 24 hours only if it is considered related to treatment.

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of underlying leukemia should be recorded as SAEs with the preferred term “chronic lymphocytic leukemia” and must be reported immediately to the sponsor.

Death is an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded on the AE form. Every effort should be made to capture the established cause of death, which may become available later on (eg, after autopsy).

9.5. Reporting of Serious Adverse Events

The investigator is responsible for reporting all SAEs observed by the investigator or reported by the subject. Unless otherwise indicated in Table 6 below, all SAEs will be reported within 24 hours and recorded in the CRF.

Table 6. Reporting Requirements for Serious Adverse Events

Subjects who are screen-fails or who are enrolled, but do not receive KITE-X19 infusion	Subjects who are enrolled and receive KITE-X19 infusion
• SAEs that occur from signing of the latest informed consent form through 30 days after the last study specific procedure (eg, screening procedure, leukapheresis, bridging therapy, conditioning chemotherapy) or until initiation of a new anti-cancer therapy, whichever occurs first, will be recorded in the CRF	• All SAEs that occur from signing of the screening informed consent form through 3 months after the KITE-X19 infusion or until initiation of another anti-cancer therapy, whichever occurs first • After 3 months, only targeted SAEs will be reported through 24 months after KITE-X19 infusion or disease progression, whichever occurs first o Targeted adverse events include central neurological events, hematological events, infections, GVHD, autoimmune disorders, and secondary malignancies. • Subjects who receive an allogeneic SCT will only be followed for KTE-X19 related SAEs. Reporting of these SAEs will commence at the time the SCT preparative regimen commences through 24 months after KTE-X19 infusion or disease progression, whichever occurs first, within 24 hours using the SAE Report Form and in the CRF. • All SAEs deemed related to KITE-X19 infusion regardless of time period • All deaths that occur from signing of the ICF through the end of study will be recorded in the CRF

Abbreviations: SAE, serious adverse event; GVHD, graft-versus-host-disease; CRF, case report form; ICF, informed consent form.
See Section 6.8 for concomitant medication and Section 9.2 for targeted AE reporting requirements.

Following completion of KTE-C19-103, any relevant information on ongoing SAEs must be submitted to Kite Patient Safety and Pharmacovigilance within 24 hours of the investigator's knowledge of the event using the paper SAE Report Form and sent via email to the SAE Reporting mailbox: safety_FC@gilead.com

Subsequently, all SAEs will be reported to the health authorities per local reporting guidelines.

9.6. Pregnancy and Lactation

There is no relevant clinical experience with KTE-X19 in pregnant or lactating women, and animal reproductive studies have not been performed. Women of childbearing potential must have a negative pregnancy test prior to enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. Women of childbearing potential should be monitored according to local and country-specific regulations. This experimental therapy should not be administered to pregnant women or women who are breastfeeding.

Female subjects and female partners of male subjects are recommended to use highly effective contraception (method must achieve an annual failure rate of < 1%) for at least 6 months after conditioning chemotherapy dosing or the administration of KTE-X19, whichever is longer. Male subjects are recommended to not father a child for 6 months after the conditioning chemotherapy dosing or the administration of KTE-X19, whichever is longer.

Any pregnancy in a female subject enrolled in the study must be reported, regardless of the time after the KTE-X19 infusion. If pregnancy occurs in a female partner of a male subject within 6 months after completing conditioning chemotherapy or the KTE-X19 infusion, whichever is longer, the pregnancy must be reported. All such pregnancies must be reported to Kite Patient Safety and Pharmacovigilance using the Pregnancy Report Form within 24 hours after becoming aware of the pregnancy. Information regarding the pregnancy and/or the outcome will be requested by Kite. Pregnancy Report Forms should be reported to Kite Patient Safety and Pharmacovigilance via email: Safety_FC@gilead.com or fax: +1 (650) 522-5477.

The pregnancy itself or an induced elective abortion to terminate a pregnancy without medical reasons are not considered AEs. Any premature termination of a pregnancy (eg, spontaneous abortion, induced therapeutic abortion due to complications, or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term. Any SAE occurring as an adverse pregnancy outcome after the study has been completed must be reported to Kite Patient Safety and Pharmacovigilance.

The pregnant subject or subject partner should receive appropriate monitoring and care until conclusion of the pregnancy. The outcome should be reported to Kite Patient Safety and Pharmacovigilance using the Pregnancy Outcome Report Form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Kite Patient Safety and Pharmacovigilance.

If a lactation case occurs in a female subject in the study, the lactation case must be reported to Kite Patient Safety and Pharmacovigilance within 24 hours after the investigator's awareness of the event using the Special Situations Reporting Form. In addition to reporting a lactation case during the study, investigators should monitor for pregnancy and lactation cases throughout the LTFU period. Report the lactation case and Special Situations Reporting Forms to Kite Patient Safety and Pharmacovigilance via email: Safety_FC@gilead.com or fax: +1 (650) 522-5477.

9.7. Safety Review Team and Dose-limiting Toxicity

The SRT, that is internal to the study sponsor and in collaboration with at least one study investigator, will be specifically chartered to review safety data from the first 3-12 subjects treated with KTE-X19 and make recommendations on further study conduct and progression of the study based on the incidence of KTE-X19 DLT and review of serious adverse events.

Dose-limiting toxicity is defined as the following KTE-X19-related events with onset within the first 28 days following KTE-X19 infusion:

- Grade 4 hematologic toxicity lasting more than 30 days (except lymphopenia) if not attributable to underlying disease

- All KTE-X19-related grade 3 non-hematologic toxicities lasting for > 7 days and all KTE-X19-related grade 4 non-hematologic toxicities regardless of duration are considered DLTs, with the exception of the following which are not considered DLTs:

- Aphasia/dysphasia or confusion/cognitive disturbance which resolves to at least grade 1 or baseline within 2 weeks and to at least baseline within 4 weeks.
- Fever grade 3 or 4
- Immediate hypersensitivity reactions occurring within 2 hours of KTE-X19 infusion (related to KTE-X19 infusion) that are reversible to a grade 2 or less within 24 hours of KTE-X19 infusion with standard therapy
- Renal toxicity which requires dialysis for ≤ 7 days
- Intubation for airway protection if ≤ 7 days
- Tumor lysis syndrome (TLS) including associated manifestations attributable to TLS (eg, electrolyte abnormalities, renal function, hyperuricemia)
- Grade 3 transaminase, alkaline phosphatase, bilirubin or other liver function test elevation, provided there is resolution to ≤ grade 2 within 14 days
- Grade 4 transient serum hepatic enzyme abnormalities provided there is resolution to ≤ grade 3 within < 72 hours
- Hypogammaglobulinemia grade 3 or 4
- Grade 3 nausea and/or anorexia

CRS will be graded according to a revised grading system {Lee 2014}. Adverse events attributed to CRS will be mapped to the overall CRS grading assessment for the determination of DLT. Consistent with non-CRS toxicities, all occurrences of grade 3 CRS of duration > 7 days and all occurrences of grade 4 CRS are considered DLTs, other than occurrences of CRS due to the exceptions listed above.

Three subjects will initially be enrolled to evaluate the safety of the KTE-X19 regimen. Subjects will be evaluated for DLTs within the first 28 days following the completion of the KTE-X19 infusion. The analysis of DLTs will be based on the DLT evaluable set as defined in Section 10.5. The SRT will make recommendations based on the incidence of DLT and overall safety profile of the KTE-X19 regimen as outlined below**:**

- If the subject incidence of DLT is 0 of 3 subjects, the SRT may recommend either
  - proceeding to Phase 2 at 2 x 10^6 anti-CD19 CAR T cells/kg; or
  - accrual of additional subjects in Phase 1 to further characterize risk/benefit prior to Phase 2
- If the subject incidence of DLT is 1 of 3 subjects, the SRT may recommend either

— accrual of an additional 3 subjects at the same cell dose with re-evaluation of the incidence of DLT after a total of 6 subjects in the DLT evaluable set have been assessed for DLT. In this case, the SRT may recommend accrual to Phase 2 if the cumulative incidence of DLT in the 6 subjects is ≤ 1 of 6 subjects; or

— evaluation of a lower dose of 1 x 10^6 anti-CD19 CAR T cells/kg in an additional set of 3-6 subjects. In this case, the SRT may recommend accrual to Phase 2 if the cumulative incidence of DLT is < 33%.

- If the subject incidence of DLT is ≥ 2 of 3 subjects, a lower dose of 1 x 10^6 anti-CD19 CAR T cells/kg in an additional set of 3-6 subjects will be explored. In this case, the SRT may recommend accrual to Phase 2 if the cumulative incidence of DLT is < 33%.

If the conditioning chemotherapy regimen and KTE-X19 dose evaluated in Phase 1 is determined to be safe based on the incidence of DLT, up to approximately 40 additional subjects (high and non-high burden disease) may be enrolled at 2 x 10^6 anti-CD19 CAR T cells/kg, 1 x 10^6 anti-CD19 CAR T cells/kg, or 0.5 x 10^6 anti-CD19 CAR T cells/kg prior to commencing Phase 2. The data from these additional subjects will be reviewed by the SRT who will provide recommendations for dose for Phase 2. Further details to be outlined in the SRT Charter.

Based on the review of all available safety and efficacy data, the benefit/risk ratio was considered most favorable at the dose of 1 x 10^6 anti-CD19 CAR T cells/kg, therefore the dose of 1 x 10^6 anti-CD19 CAR T cells/kg was considered the recommended Phase 2 dose.

The final decision to commence Phase 2 and the dose selected for Phase 2 was formally communicated to participating sites in a separate communication.

9.8. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be chartered to review safety data to make trial conduct recommendations. The DSMB will review safety data in an interim analysis during the Phase 2 portion of the study. For this interim analysis, the DSMB will review safety data after 20 Phase 2 subjects have been treated with KTE-X19 and had the opportunity to be followed for 30 days after the KTE-X19 infusion. During Phase 2, Kite Pharma or delegate will submit SAEs or suspected unexpected serious adverse reactions (SUSARs) to the DSMB chair for risk benefit analysis. The DSMB Chair will review reported SAEs at least monthly and SUSARs as soon as received. .

9.9. Criteria to Pause Enrollment

Study enrollment will be paused in Phase 1 (DLT Evaluation Period) following any grade 5 adverse event that occurs within 30 days of KTE-X19 dosing regardless of attributions. The DLT evaluation period is now complete (see Section 2.8).

As part of its oversight of the study, the DSMB also will assess criteria to pause enrollment in Phase 2 after 10, 20, and 35 subjects enrolled in Phase 2 have been treated with KTE-X19 and have had the opportunity to be followed for 30 days. Enrollment will be paused if any of the following is met:

Subject incidence of the following grade 4 KTE-X19-related adverse events lasting more than 7 days is >33%:

- Neurologic events
- CRS (per Lee 2014 criteria)
- Other non-hematological serious adverse event
- Infection (treatment-related)

10. STATISTICAL CONSIDERATIONS

10.1. Hypothesis

This study is designed to differentiate between a treatment that has a true overall complete remission rate of 40% or less and a treatment with a true overall complete remission rate of 65% or more. The hypothesis is that the overall complete remission rate to KTE-X19 is significantly greater than 40%.

A secondary endpoint, Minimum Residual Disease (MRD) Negative Rate, will be tested against a MRD-negative rate of 30% if the testing of the overall complete remission rate is significant. The hypothesis is that the MRD-negative rate to KTE-X19 is significantly greater than 30%.

10.2. Study Endpoints

10.2.1. Primary

Phase 1: Incidence of adverse events defined as dose-limiting toxicities (DLT)

Phase 2: Overall complete remission rate (CR + CRi) per independent review (Appendix 1). All subjects that do not meet the criteria for CR or CRi by the analysis data cutoff date will be considered non-responders for the overall complete remission rate evaluation.

10.2.2. Secondary

- Duration of Remission (DOR): for subjects who experience CR or CRi per independent review, DOR is defined as the time between their first complete response per indepedent review to relapse or any death in the absence of documented relapse. Relapse is defined in Appendix 1. Subjects who do not meet the criteria for relapse and who have not died will be censored at the last evaluable disease assessment or disease status follow up assessment. A sensitivity analysis will be conducted in which non-disease mortality will be considered a competing risk. Disease assessments obtained after new anti-cancer therapies (including allogeneic SCT) will not contribute to the derivation of duration of remission. The DOR for subjects that undergo allogeneic SCT while in remission is censored at the date of the allogeneic SCT; the DOR for subjects that undergo other new anti-cancer therapies in the absence of documented relapse is censored at the last evaluable disease assessment prior to the new anti-cancer therapies.

- In subjects who achieve CR, a TKI may be resumed 2 months after KTE-X19 infusion. In such subjects who resume TKI therapy, disease assessments obtained after resumption of TKI therapy will contribute to the derivation of the duration of remission. A sensitivity analysis will be conducted in which the duration of remission in such subjects is censored at the first date of the resumption of TKI therapy.

- Minimum Residual Disease (MRD) Negative Rate: The incidence of a minimal residual disease response (MRD-). MRD- is defined as MRD < 10^{-4} per the standard assessment (see Section 7.10).

- Overall complete remission rate (CR + CRi) per investigator assessment (Appendix 1).

- Allogeneic Stem Cell Transplant (Allogeneic SCT) Rate

- Overall Survival: OS is defined as the time from KTE-X19 infusion to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date.

- Relapse-free Survival (RFS): RFS is defined as the time from the KTE-X19 infusion date to the date of disease relapse or death from any cause. Subjects not meeting the criteria for relapse by the analysis data cutoff date will be censored at their last evaluable disease assessment date. Subjects who have not achieved a complete remission (CR or CRi) at the analysis data cutoff will be evaluated as having an RFS event at Day 0.

- Incidence of adverse events and CTCAE grade changes in safety laboratory values.

- Incidence of anti-KTE-X19 antibodies.

- Changes over time in the EQ-5D scale score and EQ-5D VAS score

10.2.3. Exploratory Endpoints

- Treatment related mortality rate 100 days post allogeneic stem cell transplant (TRM-Allogeneic SCT 100 day survival)Overall survival from the time of allogeneic stem cell transplant (OS-Allogeneic SCT): OS-Allogeneic SCT is evaluated in subjects who undergo allogeneic SCT and is defined as the time from allogeneic SCT to the date of death. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date.

- Complete Remission with partial Hematological Recovery (CRh). The incidence of a CRh (see Appendix 1 for definition). All subjects that do not meet the criteria for CRh by the analysis data cutoff date will not be considered to have CRh.

- Blast-free hypoplastic or aplastic bone marrow rate: The incidence of blast-free hypoplastic or aplastic bone marrow (see Appendix 1 for definition). All subjects who do not meet the criteria for blast-free hypoplastic or aplastic bone marrow by the analysis date cutoff date will not be considered to have blast-free hypoplastic or aplastic bone marrow.

- Partial remission (PR) rate: The incidence of PR (see Appendix 1 for definition). All subjects that do not meet the criteria for PR by the analysis data cutoff date will not be considered to have PR.

- The overall complete remission rate (CR and CRi), MRD-negative rate, and DOR among subjects retreated with KTE-X19
- Level and activity of CAR^+ T cells, as well presence $CD19^+$ cells in blood and bone marrow.
- Levels of cytokines in serum and CSF.

10.2.4. Covariates

The primary endpoints and selected secondary endpoints will be evaluated in subgroup analysis by subjects with or without prior blinatumomab, and by subjects with or without prior inotuzumab. Such subgroup analyses may not be performed if too few (eg, $n < 5$) subjects in the mITT set have received prior blinatumomab or prior inotuzumab at the time of the analysis.

Additional covariates and subgroup analyses will be outlined in the Statistical Analysis Plan.

10.3. Sample Size Considerations

The anticipated enrollment in this study is approximately 100 subjects.

The primary efficacy endpoint and all analyses based on the response will be based on a mITT population consisting of all subjects who receive any dose of KTE-X19 in Phase 2.

This study uses a single-arm design to test for an improvement in overall complete remission rate. For the test of efficacy this study has approximately 93% power to distinguish between an active therapy with a 65% true overall complete remission rate from a therapy with an overall complete remission rate of 40% or less with a 1-sided alpha level of 0.025. A step-down test of the secondary endpoint MRD-negative Rate will be performed against a MRD-negative rate of 30% if the testing of the overall complete remission rate is significant.

In Phase 1, the SRT will review safety data after 3 subjects in the DLT evaluable set (see Section 10.5) have had the opportunity to be followed for 28 days after the KTE-X19 infusion. If the conditioning regimen and KTE-X19 dose evaluated in Phase 1 is determined to be safe based on the incidence of DLT, up to approximately 30 additional subjects may be enrolled to further evaluate safety prior to commencing Phase 2.

During Phase 2, one interim and one primary analyses will be performed. The interim analysis is for safety only and will occur after 20 subjects have been treated with KTE-X19 and have had the opportunity to be followed for 30 days after the KTE-X19 infusion. The primary analysis will occur when the overall study enrollment is complete and all subject in the mITT set have had the opportunity to complete the month 6 disease assessment. 65% Approximately 100 subjects may be enrolled into the entire study. At the time of the primary analysis, in the event that either less than or more than 50 subjects are eligible for the mITT set, all mITT eligible subjects will be included in the analysis.

10.4. Statistical Assumptions

This study assumes that the underlying overall complete remission rate (in the absence of treatment with investigational therapy) is 40%. For MRD- rate, it is assumed that the underlying response rate (in the absence of treatment with investigational therapy) is 30%.

10.5. Analysis Subsets

KTE-X19 will be administered as a single infusion at a target dose of 2×10^6 anti-CD19 CAR T cells/kg or 1×10^6 anti-CD19 CAR T cells/kg or 0.5×10^6 anti-CD19 CAR T cells/kg . For subjects weighing greater than 100 kg, a maximum flat dose of 2×10^8 or 1×10^8 or 0.5×10^8 anti-CD19 CAR T cells/kg may be administered. Full Analysis Set: the full analysis set will consist of all enrolled subjects and will be used for summaries of subject disposition.

Modified Intention-to-treat Set (mITT): the modified intention-to-treat set will consist of all subjects enrolled in Phase 2 and treated with KTE-X19. The mITT analysis set will be used for all efficacy analyses unless otherwise specified.

DLT-evaluable set: All Phase 1 subjects treated with the target KTE-X19 dose and followed for at least 28 days, or received a dose of KTE-X19 lower than the target dose but experienced a DLT during the 28 day post infusion period, up to the time at which a dose level has been evaluated for DLT and deemed safe. Additional Phase 1 subjects enrolled and treated subsequently for the purpose of assessment of the overall safety in the same dose level or a lower dose level will not be considered as part of the DLT evaluable set, and DLT will not be assessed for such subjects.

Safety analysis set: the safety set is defined as all subjects treated with any dose of KTE-X19.

10.6. Access to Individual Subject Treatment Assignments

This is a single arm, open-label study and subjects and investigators will be aware of treatment received. Data handling procedures will be devised to reduce potential sources of bias and maintain the validity and credibility of the study. These procedures will be outlined in the study statistical analysis plan, DSMB charter, and Trial Integrity Document.

10.7. Interim Analysis

During Phase 1, the SRT will review safety data after 3 DLT evaluable subjects have had the opportunity to be followed for 28 days after the KTE-X19 infusion. The SRT will review the safety data and make recommendations on further study conduct and progression of the study as outlined in Section 9.6.

During Phase 2, the DSMB will review safety data after 20 Phase 2 subjects have been treated and followed for 30 days. The DSMB will also review SAEs on a monthly basis prior to the primary analysis. The DSMB may request additional safety data or modifying the study conduct. The sponsor may request additional reviews by the DSMB if safety concerns are identified. Data submitted to the DSMB may not have undergone completion of data cleaning procedures in order to facilitate timelines for DSMB review.

10.8. Planned Method of Analysis

The primary efficacy analysis will be performed when all subject in the mITT set have had the opportunity to complete the month 6 disease assessment. Additional analyses may occur after the primary analysis has been completed. These additional analyses will be descriptive and will occur after inferential testing has been performed. The final analysis will occur when all subjects have completed the study.

10.8.1. Overall Complete Remission Rate

The incidence of response and exact 2-sided 95% confidence intervals will be generated. An exact binomial test will be used to compare the observed response rate to a response rate of 40%.

10.8.2. Duration of Remission

Duration of Remission (DOR): for subjects who experience CR or CRi per independent review, DOR is defined as the time between their first complete response per independent review to relapse or any death in the absence of documented relapse. Relapse is defined in Appendix 1. Subjects who do not meet the criteria for relapse and who have not died will be censored at the last evaluable disease assessment or disease status follow up assessment. Disease assessments obtained after new anti-cancer therapies (including allogeneic SCT) will not contribute to the derivation of duration of remission. The DOR for subjects that undergo allogeneic SCT while in remission is censored at the date of the allogeneic SCT; the DOR for subjects that undergo other new anti-cancer therapies in the absence of relapse is censored at the last evaluable disease assessment prior to the new anti-cancer therapies. Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for DOR. Estimates of the proportion of subjects remained as in complete remission at 3-month intervals will be provided.

A sensitivity analysis of DOR will be conducted in which non-disease mortality will be considered a competing risk. A competing-risk analysis method {Klein 2005, Putter 2007} will be used to estimate the cumulative incidence of relapse. The cumulative incidence of relapse in the presence non-disease related mortality (the competing risk) will be estimated along with 2-sided 95% confidence intervals at 3-monthly time intervals.

10.8.3. MRD-negative rate

The incidence of MRD-negative rate and exact 2-sided 95% confidence intervals will be generated. If the statistical testing of the primary endpoint (overall complete remission rate) is significant, an exact binomial test will be used to compare the observed MRD-negative rate to a rate of 30% at a one-sided alpha level of 0.025.

10.8.4. CR Rate, CRi Rate, and DOR to Treatment Among Subjects Retreated with KTE-X19 for Progressive Disease after Initial Remission

The incidence of CR rate, and CRi rate, and exact 2-sided 95% confidence intervals will be generated.

DOR to retreatment is defined only for subjects who experience a CR or CRi to retreatment and is the time from the first complete remission after retreatment to relapse after retreatment or death due to disease relapse. The competing-risk analysis method will be used to estimate the cumulative incidence of relapse after retreatment.

10.8.5. Overall Survival

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for OS. Estimates of the proportion of subjects alive at 3-month intervals will be provided.

10.8.6. Allogeneic Stem Cell Transplant Rate

The incidence of Allogeneic SCT in the mITT set and 2-sided 95% confidence intervals will be generated.

10.8.7. Safety

Subject incidence rates of adverse events including all, serious, fatal, CTCAE version 4.03 grade 3 or higher and treatment related AEs reported throughout the conduct of the study will be tabulated by preferred term and/or system organ class. CTCAE grade changes in safety laboratory values will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized.

Tables and/or narratives of deaths and treatment related SAEs will be provided.

10.8.8. Long-term Data Analysis

All subjects will be followed for survival status for up to 15 years after receiving KTE-X19. LTFU data analysis will be performed on subjects in this study and after transition to the KT-US-982-5968 LTFU study. No formal hypothesis testing will be performed based on data obtained after the cutoff for the primary analysis. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

11. REGULATORY OBLIGATIONS

11.1. Independent Review Board /Independent Ethics Committee

A copy of the protocol, ICF and any additional subject or trial information such as subject recruitment materials must be submitted to each sites respective IRB/IEC for approval. Once approval is obtained from the IRB/IEC, all documents must be provided to the key sponsor contact before subject recruitment can begin.

The investigator must also receive IRB/IEC approval for all protocol and ICF changes or amendments. Investigators must ensure that ongoing/continuous IRB/IEC approval (ie, annual approval) is provided throughout the conduct of the study. Copies of IRB/IEC approval are to be forwarded to the key sponsor contact for archiving.

During the course of the study, investigators are to submit site specific and study serious adverse events (provided to the site by the key sponsor contact) along with any protocol deviations to their IRB/IEC in accordance with their respective IRB/IEC policies.

11.2. Subject Confidentiality

Subject confidentiality must be contained at all material submitted to the key sponsor contact. The following rules are to be applied.

- Subjects will be identified by a unique identification number
- Date of birth or year of birth/age at time of enrollment will be reported according with local laws and regulations

For reporting of serious adverse events, subjects will be identified by their respective subject identification number, initials and data of birth (as per their local reporting requirements for both initials and date of birth)

Per federal regulations and ICH/GCP guidelines, investigators and institutions are required to permit authorization to the sponsor, CRO, IRB/IEC and regulatory agencies to subject's original source documents for verification of study data. The investigator is responsible for informing potential subjects that such individuals will have access to their medical records which includes personal information.

11.3. Investigator Signatory Obligations

Each clinical study report will be signed by the coordinating investigator. The coordinating investigator will be identified by Kite Pharma under the following criteria:

- A recognized expert in the disease setting
- Provided significant contributions to the design or analysis of study data
- Participate in the study and enrolled a high number of eligible subjects

12. PROTOCOL AMENDMENTS AND TERMINATION

If the protocol is amended, the investigators agreement with the amendment and the IRB/IEC approval of the amendment must be obtained. Documentation acknowledging approval from both parties are to be submitted to the key sponsor contact.

Both Kite Pharma and the investigator reserve the right to terminate the investigators participation in the study as per the terms of the agreement in the study contract. The investigator is to provide written communication to the IRB/IEC of the trial completion or early termination and provide the CRO with a copy of the correspondence.

Kite Pharma reserves the unilateral right, at is sole discretion, to determine whether to manufacture KTE-X19 T cells and provide them to sites and subjects after the completion of the study and before treatment becomes commercially available.

13. STUDY DOCUMENTATION AND ARCHIVE

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. These individuals authorized to fulfil these responsibilities should be outlined and included in the Delegation of Authority Form.

Source documents are original documents, data and records for which the study data are collected and verified. Example of such source documents may include, but are not limited to, hospital records and patient charts, laboratory, pharmacy, radiology and records, subject diaries, microfiches, correspondence and death registries. Case report form entries may be considered as source data if the site of the original data collection is not available. However use of the CRFs as source documentation as a routine practice is not recommended.

The investigator and study staff are responsible for maintaining a comprehensive and centralize filing system of all subject records that are readily retrieved to be monitored and or audited at any time by the key sponsor contact, regulatory authorities and IRB/IECs. The filing system will include at minimum:

- Subject content including ICFs and subject identification lists
- Protocols and protocol amendments, investigator brochure, copies of pre-study documentation, and all IRB/IEC and sponsor communication
- Proof of receipt, experimental treatment flow records and experimental product related correspondence.

Original source documents supporting entries into CRFs must be maintained at the site and readily available upon request. No study documents should be discarded without prior written agreement between Kite Pharma and the investigator. Should storage no longer be available to archive source documents or must be moved to an alternative location, the research staff should notify the key sponsor contact prior to the shipping the documents.

14. STUDY MONITORING AND DATA COLLECTION

The key sponsor contact, monitors, auditors or regulatory inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and verifying source documents and records assuring that subject confidentially is respected.

The monitor is responsible for source document verification of CRF data at regular intervals during the study. Protocol adherence, accuracy and consistency of study conduct and data collection with respect to local regulations will be confirmed. Monitors will have access to subject records as identified in Section 13.

By signing the investigator agreement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits.

In accordance with ICH GCP and the audit plan, a site may be chosen for a site audit. A site audit would include, but is not limited to, an inspection of the facility (ies), review of subject and study related records, and compliance with protocol requirements as well as ICH GCP and applicable regulatory policies.

All data will be collected in an electronic CRF system. All entries must be completed in English and concomitant medications should be identified by tradenames. For further details surrounding the completion of CRFs, refer to the CRF completion guidelines.

15. PUBLICATION

Authorship of publications from data generated in study KTE-C19-103 will be determined based on the uniform requirements for manuscripts submitted to biomedical journals (as outlined in the International Committee of Medical Journal Editors December 2013) which states:

- Authorship should be based on
  - — Substantial contributions to the conception or design of the work, acquisition of data, analysis, or interpretation of data for the work AND
  - — Drafting the article or revising it critically for important intellectual content; AND
  - — Final approval of the version to be published; AND
  - — Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work re appropriately investigated or resolved

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. This individual should fully meet the criteria for authorship defined above.

Funding, collection of data or general supervision of the research alone or in combination does not qualify an individual for authorship.

Any publication, in any form, that is derived from this study must be submitted to Kite Pharma for review and approval. The study contract between the institution, principal investigation and Kite Pharma or its delegate will outline the requirements for publication review.

16. COMPENSATION

Kite Pharma will provide compensation for study related illness or injury pursuant to the information outlined in the injury section of the ICF.

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18. APPENDICES

Appendix 1. OVERALL DISEASE RESPONSE CLASSIFICATION

Response	BM		Peripheral Blood [d]		CNS EMD		Non-CNS EMD [b, e]
CR	≤ 5% [f]	*and*	ANC ≥ 1,000 and Plt ≥ 100,000	*and*	CNS-1	*and*	CR [c]
CRi			ANC ≥ 1000 and Plt < 100,000 OR ANC < 1000 and Plt ≥ 100,000				
CRh			ANC ≥ 500 and Plt ≥ 50,000 but not CR				
Blast-free hypoplastic or aplastic BM			Any values not meeting criteria for CR, CRi or CRh				
PR	All criteria for CR, CRi, CRh or blast-free hypoplastic or aplastic bone marrow are met					*and*	PR
Relapse	>5% [f]	*or*	Circulating leukemia present [a]	*or*	CNS-2 or CNS-3	*or*	PD
No response	All required assessments are performed with failure to attain the criteria needed for any response category						
Unknown	Assessment is not done, incomplete, or indeterminate Note: Overall disease response can be assessed as 'Relapsed disease' if any single element of disease response assessment shows relapse, other Unknown elements of disease response assessment do not need to be evaluated						

ANC = absolute neutrophil count; BM = bone marrow; EMD = extramedullary disease; Plt = platelets;

a No circulating leukemia is < 1% circulating blasts by morphology; Circulating leukemia is ≥ 1% circulating blasts by morphology; If ≥ 1% blast by morphology and there is no other evidence of leukemia, then flow or molecular studies should be conducted to confirm that blasts are leukemia.

b See Overall Non-CNS EMD table (Appendix 2)

c If baseline EMD is present, then images must show CR. If no baseline EMD, then images are not required, but if performed, must show CR per Appendix 2.

d ANC and Plt: The units for Plt and ANC are per uL. ANC and Plt values should be evaluated every time a BM evaluation is performed. If not done, ANC and Plt values used for response assessment can be from any time 7 days prior to the BM result to any time after the BM result.

e In subjects evaluated for non-CNS EMD, imaging and bone marrow results used for assessment of overall disease response must be within 30 days of each other

f Blasts by morphology in BM

Appendix 2. EXTRAMEDULLARY DISEASE RESPONSE

Subjects with known baseline extramedullary disease (EMD) should have disease assessed by the investigator per the Table below at baseline and post-baseline with an imaging modality appropriate for the anatomical site and clinical scenario (eg, MRI for CNS lesion, ultrasound for testicular lesion, CT for intra-abdominal or thoracic lesion) and with the same imaging modality throughout.

Response [a]	PET Baseline, On-study		Baseline lesion(s) (by CT or MRI) [b]		New Lesion(s)

CR	Neg, N/A	*and*	All of:
			• Disappearance of measurable and non-measurable nodal lesions:
			  ○ Nodal masses >1.5 cm in greatest transverse diameter (GTD) at baseline must have regressed to ≤1.5 cm in GTD
			  ○ Nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to 1.0cm in their short axis after treatment
			• If testes, spleen and/or liver involvement, they must be normal size by imaging or physical examination.
				and	No

	Pos, Neg	*and*	Any	*and*	No
PR	Any	*and*	All of: • ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant masses. Dominant masses should be clearly measurable in at least 2 perpendicular dimensions, and should be from different regions of the body if possible. • No increase in size of liver or spleen by imaging or physical exam • If multiple splenic and hepatic nodules are present, they must regress by ≥ 50% in the SPD. There must be a > 50% decrease in the greatest transverse diameter for a single nodule.	*and*	No
SD	Does not meet the criteria for CR, PR, or PD				
PD	Any	*and*	At least one of the following: • ≥ 50% increase from nadir in the sum of the products of at least two lymph nodes, or if a single node is involved at least a 50% increase in the product of the diameters of this one node. • At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis • Greater than or equal to a 50% increase in size of splenic, hepatic or any other non-nodal lesion.	*or*	Yes

Neg = Negative; Pos = Positive; N/A = Not applicable
a Modified Revised IWG Criteria {Cheson 2007}
b see Section 7.9.2 of protocol for details.

Appendix 3. SCHEDULE OF ASSESSMENTS FOR GERMAN SUBJECTS FOLLOWING KTE-X19 INFUSION

The post-infusion monitoring of subjects, described in section 7.11.7.2 in this protocol, will be extended by monitoring on Day 8, Day 9, and Day 10, according to procedures outlined in the Schedule of Assessment Table, column "IP administration period, 1-7". The subject may stay hospitalized or return to the clinic daily for this extended monitoring at the discretion of the investigator.

The daily monitoring will include vital signs (see section 7.4), blood draw for chemistry panel with CRP, ferritin (and LDH if indicated as per section 7.11.7.4), blood draw for CBC w/differential, and neurological assessment (see section 7.5). Any observed toxicity will be managed according to section 6.10 of this protocol.

NON-INTERVENTIONAL STUDY PROTOCOL

Study Title:	LONG-TERM, NON-INTERVENTIONAL STUDY OF THE TREATMENT BY TECARTUS OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY (R/R) B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)
Short Title:	Tecartus ALL Post Authorization Study
Marketing Authorization Holder:	Kite Pharma EU B.V.
EU PAS Register No.:	Will be entered after EU PAS (European Union Post-Authorisation Studies) registration.
Clinical Trials.gov Identifier:	Study not registered
Indication:	Acute Lymphoblastic Leukemia
Active substance:	Brexucabtagene autoleucel (KTE-X19)
Medicinal Product:	Tecartus®
Product reference:	EMEA/H/C/005102
Procedure number:	EMEA/H/C/005102
Joint PASS (Post-Authorization Safety Study) :	No

Research Question and Objectives:	Primary objective: To evaluate the effectiveness of Tecartus treatment in relapsed/refractory (r/r) B-cell precursor ALL in terms of overall complete remission (OCR) rate (complete remission + complete remission with incomplete hematologic recovery). Secondary objectives: Effectiveness will be evaluated as follows: • To determine the overall survival (OS) rate and causes of death after administration of Tecartus. • To evaluate duration of remission (DOR). • To evaluate time to next treatment (TTNT). • To assess OCR rate, OS, DOR, and TTNT by gender and age, and in special populations (patients with prior allogeneic stem cell transplantation [allo-SCT], patients who receive a subsequent allo-SCT and patients treated with Out of Specifications [OOS] product). Safety will be evaluated as follows: • To evaluate the incidence rate and severity of adverse drug reactions (ADRs) in patients treated with Tecartus, including secondary malignancies, Cytokine Release Syndrome, neurologic events, serious infections, prolonged cytopenias, and hypogammaglobulinemia. • To assess the safety profile by gender and age, and in special populations (patients with prior allo-SCT, patients who receive a subsequent allo-SCT and patients treated with OOS product); additional subgroups may also be explored. • To assess the risk of tumor lysis syndrome and aggravated Graft Versus Host Disease. The other exploratory objectives of this study are as follows: • To evaluate pregnancy outcomes in female patients of childbearing potential.

Country (-ies) of study:	In countries where Tecartus will be commercially available. At a minimum Great Britain, Spain, Switzerland, and Germany will be countries of study; further countries may be added.
Protocol ID:	KT-EU-474-6644
Protocol Version/Date:	[Draft 0.2]: [31 October 2022]
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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
ALL	Acute lymphoblastic leukemia
allo-SCT	allogeneic stem cell transplantation
ANC	Absolute neutrophil count
CALGB	Cancer and Leukemia Group B
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CDR	Complimentary determining regions
CI	Confidence interval
CNS	Central nervous system
CR	Complete remission
CRi	Complete remission with incomplete hematologic recovery
CRS	Cytokine release syndrome
DOR	Duration of response
EBMT	European Society for Blood and Marrow Transplantation
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GB	Great Britain
GLPS	Global Patient Safety
GvHD	Graft versus Host Disease
GVP	Good Pharmacovigilance Practices
HCP	Health care professional
HLA	Human Leukocyte Antigen
Ig	Immunoglobulin
IRB	Institutional Review Board
mAb	Monoclonal antibody
MCL	Mantle cell lymphoma
MRD	Minimal residual disease
OCR	Overall complete remission
OOS	Out of specifications
ORR	Overall response rate
OS	Overall survival
PAS	Post Authorization Study
Ph+/-	Philadelphia chromosome positive/negative
RCR	Replication competent retrovirus
r/r	relapsed/refractory
SADR	Serious adverse drug reaction
SAE	Serious adverse event

scFv	Single-chain variable fragment
SCT	Stem cell transplantation
SOC	Standard of care
SSR	Special situation report
TCR	T-cell receptor
TKI	Tyrosine kinase inhibitor
TLS	Tumor lysis syndrome
TTNT	Time to next treatment
US	United States

PROTOCOL SYNOPSIS
Kite Pharma Inc.
Address: 2400 Broadway Santa Monica, CA 90404 USA

Study Title:	LONG-TERM, NON-INTERVENTIONAL STUDY OF THE TREATMENT BY TECARTUS OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY (R/R) B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)
Short Title: [Short Title]	Tecartus ALL Post Authorization Study
EU PAS Register No **ClinicalTrials.gov Identifier**	Will be entered after EU PAS (European Union Post-Authorisation Studies) registration Study not registered
Rationale and Background:	This is a non-interventional study based on secondary use of data collected within the infrastructure created by the European Society for Blood and Marrow Transplantation (EBMT) (i.e. the EBMT Registry) to systematically capture information at the time of Tecartus infusion and during follow-up. The follow-up period will be 15 years for the safety cohort. The effectiveness cohort will be analyzed once 200 recipients of Tecartus have been documented for ALL in the EBMT Registry. The effectiveness cohort will also be analyzed for safety assessments and 300 patients will be included in the safety cohort. As this is a study based on secondary use of data collected under 'real-world' conditions, effectiveness will be evaluated, which refers to study drug's performance under "real-world" settings. Rationale for the effectiveness cohort: To determine effectiveness of treatment with Tecartus, which includes overall complete remission (OCR) rate overall survival (OS), duration of response (DOR), and Time to next treatment (TTNT) Rationale for the safety cohort: To capture long-term follow-up data for recipients of Tecartus to evaluate the safety, as well as the known and potential risks associated with this product, including incidence rates and severity of adverse drug

	reactions (ADRs), long term safety, and risk of subsequent neoplasm.
Research Question and Objectives:	The primary objective of this study is as follows: • To evaluate the effectiveness of Tecartus in terms of OCR rate (complete remission [CR] + complete remission with incomplete hematologic recovery [CRi]). The secondary objectives of this study are as follows : Effectiveness will be evaluated as follows: • To determine the OS rate and causes of death after administration of Tecartus. • To evaluate DOR. • To evaluate TTNT. • To assess OCR rate, OS, DOR, and TTNT by gender, age, and in special populations (patients with prior allogeneic stem cell transplantation [allo-SCT], patients who receive a subsequent allo-SCT and patients treated with Out of Specifications [OOS] product). Safety will be evaluated as follows: • To evaluate the incidence rate and severity of ADRs in patients treated with Tecartus, including secondary malignancies, cytokine release syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, and hypogammaglobulinemia. • To assess the safety profile by gender and age, and in special populations (patients with prior allo-SCT, patients who receive a subsequent allo-SCT and patients treated with OOS product); additional subgroups may also be explored. • To assess the risk of tumor lysis syndrome (TLS) and aggravated graft versus host disease (GvHD). The other exploratory objectives of this study are as follows: • To evaluate pregnancy outcomes in female patients of childbearing potential.
Study Design:	This is a long-term, non-interventional study of adult patients [26 years of age and above in the European

	Union (EU) (and Great Britain (GB)] treated with Tecartus for r/r B-cell precursor ALL. Patients' data might be entered into the EBMT Registry up to 1 week prior to or anytime following Tecartus infusion. Patients will be followed in the EBMT Registry for both study assessments. For the safety assessment, 300 patients will be followed for up to 15 years; for the effectiveness assessment, patients will be followed until the first 200 eligible patients treated with Tecartus have been documented in the EBMT Registry (expected approximately 4 years after start of data collection). As this is a study based on secondary use of data collected in the EBMT Registry, expedited reporting of individual case safety reports will not be required. For the reporting of safety data, the centers will follow the standard spontaneous reporting system per local regulations and timelines
Study Size:	Effectiveness assessment: The first 200 eligible patients who have been treated with Tecartus and documented in the EBMT Registry will be included. Approximately 4 years after the start of data collection 200 patients are expected to have been documented in the EBMT Registry. Safety assessment: The first 300 eligible patients who have been treated with Tecartus and documented in the EBMT Registry will be included. Approximately 5 years after the start of data collection 300 patients are expected to have been documented in the EBMT Registry. In addition to the further characterization of the immediate and established safety profile of Tecartus, the study will evaluate rare and delayed safety events occurring in patients during 15 years of follow-up. Based on a projection of 300 eligible patients, the available person-years of follow-up are approximated using a piecewise linear survival curve with 2-year survival rate of 56% (assumption based on the primary analysis of ZUMA-3 phase 2 July 2021 data cut) and an assumption of long term 15-year survival rate of 30%, indicating an average person-years of follow-up of 7.14 years. Kite also assumes 10% overall loss to follow-up, resulting in approximately 1927.8 total

	person-years of follow-up. This number of person-years of follow-up will provide 93%, or 73%, or 58%, or 48%, or 40% likelihood of seeing at least one event of interest, if the true rate per 15 years of exposure is at least 1:50, or 1:100, or 1:150, or 1:200, or 1:250, respectively.
Study Population:	The population comprises adult patients receiving Tecartus for r/r B-cell precursor ALL at participating centers who consent to have data reported to the EBMT.
Main Eligibility Criteria:	The EBMT Registry collects data on all patients receiving cell therapy. Eligible patient data for this study is from adult patients (aged 26 years of age and above in the EU and GB) treated with Tecartus for r/r B-cell precursor ALL. Patients must consent to share clinical data with EBMT. Patients participating in interventional clinical trials at the same time will not be included in this study.
Study Period/Follow-up	Study period will be approximately 4 years for effectiveness cohort, 20 years (5 years of enrolment and 15 years of follow-up) for safety cohort
Variables:	This non-interventional, secondary use of data study makes use of the EBMT Registry and is dependent on all needed variables to be collected in the EBMT Cellular and Gene Therapy Form • Variables collected for analysis of the Primary Objective and Effectiveness Objectives

	— OCR and date of remission evaluated — Additional treatment and date of treatment received for primary disease (r/r ALL) after Tecartus administration — Date and main cause of death, or date of the last day known being alive • Variables utilized for analysis of Safety Objectives — Secondary malignancy (date of diagnosis, type and location) — CRS (grade, grade system, date of onset, treatment and resolution status) — Neurologic toxicity (type, grade, grade system, management including treatment, date of onset and resolution status of all neurologic toxicities) — Prolonged cytopenias are defined as inability to recover the absolute neutrophil count (ANC) and platelets within 30 days after the administration of Tecartus. ANC recovery is defined as neutrophil count $\geq 500/mm^3$ for 3 consecutive values, and platelet recovery is defined as platelet count $\geq 50 \times 10^9/L$ without transfusion support within 7 days. Date of recovery will be collected for ANC and platelets. — Serious infections (type, organism, treatment and date of onset of infection as well as resolution status) — Hypogammaglobulinemia is defined as serum Immunoglobulin (Ig) G levels below 600 mg/dL. Date of onset, treatment, and resolution status will be collected. — Grade, date of onset, treatment and resolution of TLS — Type, date of onset, and resolution status of aggravated GvHD. For acute GvHD in addition: grade and relationship to cell therapy • Variables utilized for analysis of Other Exploratory Objectives

	— Pregnancy that occurs after administration of Tecartus and additional information related to the outcome of the pregnancy and the newborn's health • Variables utilized for analysis of exposure to Tecartus — Name and dose level of lymphodepleting chemotherapy received prior to Tecartus infusion — Tecartus infusion: date, and whether Tecartus was released at physician's request, because the manufactured product was out of specification • Demographics and baseline characteristics — Age, gender, and country — Height and weight at the time of Tecartus infusion — Prior lines of treatment and response — Disease stage at time of cellular therapy — Time from diagnosis of the primary disease to cellular therapy — Prior hematopoietic stem cell transplantation (SCT): autologous or allogeneic, donor human leukocyte antigen (HLA) match type (HLA-identical sibling, syngeneic, HLA-matched other relative, HLA-mismatched relative), source of stem cell product (umbilical cord blood, bone marrow, peripheral blood), immunosuppressants (type and duration), prior GvHD. — Prior cellular therapy (other than allo-SCT) — Performance score (Eastern Cooperative Oncology Group or Karnofsky) — Comorbidities index (Sorror score) — Active autoimmune, neurologic and hematological disease; infection related complications

Data Sources:	For this specific protocol: patient data as available within the EBMT Registry.
Data Analysis:	Analysis of all endpoints for this study will include all patients who satisfy the eligibility criteria, are documented within the EBMT Registry and are treated with Tecartus for r/r B-cell precursor ALL. Categorical variables will be summarized descriptively by number and percentage of patients in each categorical definition with 95% confidence intervals. Continuous variables will be summarized descriptively by mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum. Patient incidence of endpoint events will be provided. Multivariate Poisson regression analyses will be used to estimate cumulative incidence rates adjusted for the follow-up period and predefined characteristics, to estimate their prognostic effect on the outcome. Kaplan-Meier curves will be used to illustrate all time-to-event data. The competing risk analysis method will be used for the analysis of time to onset and duration of endpoint events, and TTNT and the cumulative incidence at specified time points will be provided. Cox proportional hazard models will be used to model multivariate time-to-event data adjusted for predefined subgroups and other potential confounders to estimate their prognostic effect on the outcome. Effectiveness assessment: The analysis of the effectiveness endpoints will be conducted when effectiveness data from approximately 200 eligible patients has been documented. • Primary Endpoint — OCR rate • Other effectiveness Endpoints — OS — DOR — TTNT

	— Effectiveness endpoints (OCR rate, OS, DOR, TTNT) by gender and age (including the age subgroups 18-25 years, 26-59 years and 60+ years of age) — Effectiveness endpoints (OCR rate, OS, DOR and TTNT) in special populations (patients with prior, or patients who receive subsequent allo-SCT, and patients treated with OOS product) • Safety Endpoints — Incidence rates, time to onset, type and location of secondary malignancy — Incidence rates, severity, time to onset, management and resolution of CRS — Incidence rates, severity, time to onset, management and resolution, and type of neurologic events — Incidence rates of prolonged cytopenias and time to recovery of ANC and platelets — Incidence rates, type, organism, resolution, and time to onset of serious infections — Incidence rates, time to onset of hypogammaglobulinemia, and use of replacement Ig therapy — Safety endpoints on subgroups by gender, age, and in special populations (patients who receive a subsequent allo-SCT, patients treated with OOS product), and additional subgroups may also be explored — Incidence rate, severity, resolution, and time to onset of TLS — Incidence rate, resolution, time to onset of aggravated GvHD by acute and chronic type; incidence rate, severity and relationship to cell therapy for acute GvHD • Other Exploratory Endpoints — Occurrence of pregnancy and pregnancy outcome among women with childbearing potential

PLANNED MILESTONES

Table 1. Planned Milestones

Milestone	Planned Date
Approval (EC Decision) of study protocol	To be determined
Protocol registration in the EU PAS Registry	2 weeks after EC decision
Start of data collection*	6 months after EC decision
End of data collection effectiveness cohort**	4.5 years after EC decision
End of data collection safety cohort***	20.5 years after EC decision
Study duration	20 years
Annual reports effectiveness cohort	Annually for 3 years for effectiveness assessment
Final Report for Effectiveness Cohort	Approx. 5.25 years after start of data collection
Annual reports safety cohort	Annually for 5 years after start of data collection, then every 2 years for safety assessment
Final Report of Study Results	21 years after EC decision

Abbreviations: EBMT: European Society for Blood and Marrow Transplantation), EC: European Commission, EU PAS Registry: European Union electronic Register of Post-Authorisation Studies
* As the data collection in the EBMT Registry is independent of this study (secondary use of data), the start of data collection is the date from which data extraction starts. First data extraction for the study will take place 3 months after protocol registration or contract execution with the EBMT, whichever comes last.
** When effectiveness data from approximately 200 eligible patients are documented.
*** 20 years after protocol registration, no further data will be included in the study analyses.

1. INTRODUCTION

1.1. Background

1.1.1. Overview of Acute lymphoblastic leukemia and Epidemiology

Acute lymphoblastic leukemia (ALL) is a heterogeneous group of lymphoid disorders that results from the clonal proliferation of immature lymphocytes of B-cell or T-cell lineage in the blood, bone marrow, and other organs. The disease occurs with a bimodal age distribution, with 60% of cases diagnosed in patients less than 20 years old, and 25% of cases diagnosed at age 45 years or greater. In the United States (US) there are approximately 6,000 new ALL cases diagnosed per year, of which 2,500 are in adults. While 5-year survival rates are 80-90% in children, less than 25% of adults achieve long-term survival, and the majority of the 1,400 ALL deaths per year in the US are in adults{National Comprehensive Cancer Network 2014}; {Kantarjian 2004}; {Pulte 2014} {Sive 2012} {Siegel 2014}. While initial complete response (CR) rates in adults are high (80-90%) and the median duration of first remission in most studies is 18 months or longer, most patients eventually experience relapse {Kantarjian 1994}; {Kantarjian 2004, Larson 1995, Rowe 2005}. Outcomes in the second line and beyond setting with chemotherapy are poor with CR rates of approximately 20-40%, being lower in patients with relapse within 12 months of initial response, and overall survival (OS) being approximately 6 months, making the relapsed/refractory (r/r) setting the area of greatest unmet need in ALL {Faderl 2011, Fielding 2007, Kantarjian 2003, O'Brien 2013, Tavernier 2007, Thomas 1999}

Diagnosis of ALL requires at least 20% lymphoblasts in the bone marrow {Harris 1999}. ALL is then classified into 1 of 3 major subtypes by immunophenotyping: B-cell precursor ALL (70%), mature B-cell ALL (Burkitt lymphoma; 5%), and T-cell ALL (25%). B-cell ALLs are generally Cluster of differentiation (CD)10+, CD19+, and CD79a+, although precursor B-cell ALLs may be CD10-. Mature B-cell ALLs additionally express surface immunoglobulin (Ig). T-cell ALLs express T-cell markers such as CD3, CD4, and CD8. The 3 immunophenotypic subtypes are associated with non-overlapping prognoses and treatments making the classification clinically relevant {National Comprehensive Cancer Network 2014}. B-cell precursor ALL comprises the majority of all adult ALL cases.

Several anti-neoplastic agents are given in varying doses and schedules based on regional preferences and patient tolerability in 3 distinct phases for first-line treatment: induction, intensified consolidation, and maintenance. Central nervous system (CNS) prophylaxis accompanies induction and consolidation. The goals of treatment are to reconstitute normal hematopoiesis, prevent emergence of resistant subclones, eliminate minimal residual disease (MRD), and provide prophylaxis to sanctuary sites. Allo-SCT also plays a role in the management of ALL, and tyrosine kinase inhibitors (TKI) are added to chemotherapy and transplant regimens in patients with Philadelphia chromosome positive (Ph+) disease.
Most first-line regimens 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

TKI such as imatinib is included in the treatment regimen for patients with Ph+ disease. Dexamethasone appears to decrease the risk of CNS relapse and improve EFS compared to prednisone, but at the risk of increased toxicity and no OS advantage {Mitchell 2005}; {Pui 2006}. The hyper-CVAD regimen which has demonstrated efficacy in ALL, is a variation on the CALGB regimen with alternating regimens of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone with high-dose methotrexate and cytarabine {Kantarjian 2004}. First-line regimens yield CR rates of 80-90% in adults. Despite the high CR rates and a median duration of first remission of at least 18 months, many adult patients eventually relapse.

The salvage setting represents the area of greatest need in adult ALL given the poor outcomes achieved with chemotherapy in adults who have r/r ALL. Second-line chemotherapy yields remissions in about 20-40% of patients, with the remission rate being lower in patients who relapse within 12 months of an initial response.

In the third line and beyond setting, CRs with chemotherapy are seen in at most 20% of patients, and the majority of remissions are short lived {Thomas 1999}; {Kantarjian 2003}; {Fielding 2007}; {Tavernier 2007}; {Faderl 2011}; {O'Brien 2013}. Although long-term disease-free survival rates of allo-SCT are superior to chemotherapy in the salvage setting (approximately 40% vs 20%), only 30-40% of patients who achieve a second CR are eligible for SCT, and fewer than half of the patients who achieve a second CR have enough time prior to relapse to make it to transplant {Herzig 1987}; {Kolb 2009}; {Terwey 2009}, with rates as low as 5% in adults being reported in some series {Thomas 1999}

In December 2014, the bispecific CD19-directed CD3 T-cell engaging agent blinatumomab was granted accelerated approval in the US for the treatment of Ph- r/r B-cell recursor ALL (blinatumomab USPI). The approval was granted based primarily on findings from a single-arm study of 185 evaluable patients with r/r B-cell precursor ALL (relapsed with first remission duration of ≤12 months in first salvage or r/r after first salvage therapy or relapsed within 12 months of SCT). CR was achieved in 32% of patients, and an additional 9% had CR with partial hematologic recovery (CRh). The majority of responses (81%) occurred within Cycle 1 of treatment, 75% of those with CR/CRh had a MRD-negative response, and the SCT rate among those who achieved CR/CRh was 39%. Duration of response (DOR)/relapse-free survival in patients who had CR/CRh was 5.9 months. Results from a second study of blinatumomab, a Phase 3 trial which randomized adults with r/r ALL 2:1 to blinatumomab versus 1 of 4 standard of care (SOC) chemotherapy regimens, confirmed clinical benefit of blinatumomab. A total of 405 patients were randomized, and a prespecified interim analysis occurred after 248 deaths. Median OS was 7.8 months [95% Confidence interval (CI): 5.7, 10.0] for blinatumomab and 4.0 months (95% CI: 2.9, 5.4) for SOC (p=.011; hazard ratio=0.71), surpassing the prespecified boundary p-value of 0.0183. Based on these results, this study was terminated early upon the recommendation of the study's Data Safety Monitoring Board {Topp 2016}.

1.2. Rationale for the Study

T cells play a central role in the immune system by destroying diseased cells, including tumor cells, throughout the body {Kershaw 2013}. Studies with tumor vaccines{Kantoff 2010}, immune checkpoint inhibitors {Hamid 2013, Wolchok 2013}, tumor infiltrating lymphocytes

{Rosenberg 2011}, the bispecific CD19-directed CD3 T-cell engager blinatumomab {BLINCYTO 2019}, and chimeric antigen receptor (CAR) T-cells {KYMRIAH 2018, YESCARTA 2019a, YESCARTA 2019b} have demonstrated the potential of T cells to treat cancer.

Engineered autologous T cell immunotherapy, which uses a patient's own immune cells, offers a promising approach for treating many types of cancer. One type of engineered autologous T cell therapy comprises T cells that have been engineered ex vivo to express a CAR directed toward a tumor surface antigen. These CARs are fusion proteins with antigen-binding, transmembrane, and T cell activation domains that, when expressed in T cells, can target tumor antigens for T cell-mediated killing {Kershaw 2013}. CAR T cells have demonstrated promising antitumor activity across numerous B-cell malignancies, including non-Hodgkin lymphoma {Kochenderfer 2012}, {Kochenderfer 2015}, {Kochenderfer 2017, Li 2009}, {Locke 2019} {Neelapu 2017} {Turtle 2016} chronic lymphocytic leukemia {Kochenderfer 2015}, {Porter 2015}, {Porter 2011}, and ALL {Davila 2014}, {Gupta 2007}, {Lee 2015}, {Maude 2014}, {Maude 2015}, {Singh 2016}.

1.2.1. Anti-CD19 CAR T cell Product: Tecartus

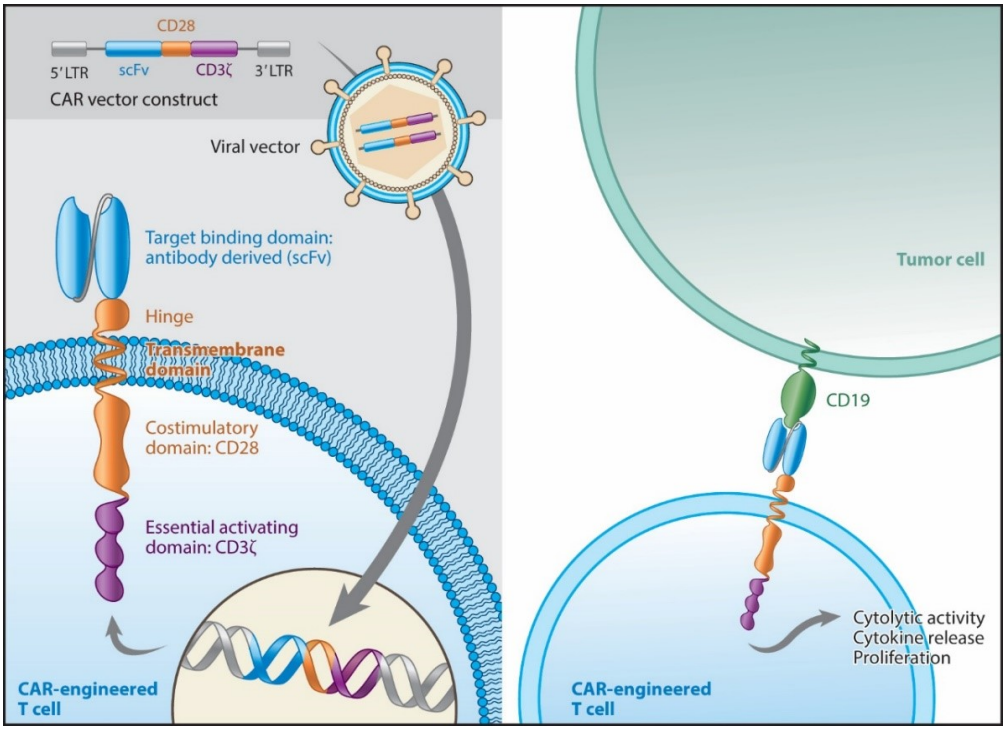
Tecartus is an autologous CAR T-cell therapy that targets CD19, a 95 kD transmembrane protein that is uniquely expressed in normal B-cells and in most B-cell malignancies {Anderson 1984}, {Johnson 2009}, {Leonard 2001}, {Nadler 1983}, {Olejniczak 2006}, {Rodriguez 1994}, {Uckun 1988}. Expression occurs beginning at the pro-B-cell stage and continues throughout B-cell differentiation {Anderson 1984}, {Nadler 1983}, {Uckun 1990}, {Uckun 1988}, but is down regulated in plasma cells {Gupta 2009},{Lin 2004}. CAR T-cell therapies have demonstrated antitumor activity across numerous B-cell malignancies, including ALL {Davila 2014}, {Gupta 2007}, {Lee 2015}, {Maude 2014}, {Maude 2015}, {Singh 2016}

Kite Pharma, Inc. has developed manufacturing processes to meet the needs of patients with B-precursor leukemias, such as ALL, as well as advanced B-cell lymphomas, such as Mantle cell lymphoma (MCL), characterized by different types of B-cell malignancies. Tecartus first received approval on 24 July 2020 from the US Food and Drug Administration Accelerated Approval pathway for the treatment of adult patients with r/r MCL (BL 125703/0). Tecartus was granted conditional marketing authorization from the European Commission on 14 December 2020 for the treatment of adult patients with r/r MCL after two or more lines of systemic therapy including a Bruton's TKi (EMEA/H/C/005102) and has since been granted marketing authorisation for this same indication in Australia, Canada, Great Britain (GB), Israel, and Switzerland.

Tecartus was subsequently approved in the US and Australia for the treatment of adult patients with r/r B-cell precursor ALL. On 02 September 2022, the European Commission approved Tecartus for the treatment of adult patients 26 years of age and above with r/r B-cell precursor ALL.

The structure of the anti-CD19-CAR construct used for production of Tecartus and the product's mechanism of action are shown in Figure 1. Briefly, the construct comprises the following domains: an antihuman CD19 single-chain variable fragment (scFv) region; the partial extracellular domain and complete transmembrane and intracellular signaling domains of human CD28; and the cytoplasmic portion, including the signaling domain, of human CD3ζ, a component of the T-cell receptor (TCR) complex.

Figure 1. Tecartus CAR Construct and Mode of Action



Abbreviations: CAR: chimeric antigen receptor; CD: cluster of differentiation; LTR: long terminal repeat; scFv: single-chain variable fragment
General notes: The left panel illustrates the Tecartus construct with scFv/CD28/CD3ζ, which is inserted in a replication incompetent γ-retroviral vector and, upon transfection of T cells, expresses the chimeric transmembrane protein. The right panel illustrates the antiCD19 CAR T-cell binding to its target CD19 on the tumor cell surface.

The CAR antigen-binding domain is an scFv derived from the FMC63 murine monoclonal antibody (mAb) directed against human CD19 {Nicholson 1997}. This antigen-binding domain extends from the engineered T-cell membrane into the extracellular space, where it can recognize CD19, its target antigen. The antigen-binding domain of the anti-CD19 CAR construct encompasses the following domains, in order from the N-terminal end towards the membrane proximal region: the FMC63 antibody light-chain variable domain (complementary determining regions [CDR] 1 and 2); a peptide linker {Cooper 2003}; and the FMC63 antibody heavy chain variable domain (CDR1, CDR2, and CDR3). This folding retains the selectivity and affinity of the parent FMC63 mAb. Extensive comparative analyses {Nicholson 1997}demonstrated that the specificity of the scFv was equivalent to that of the original FMC63 mAb {Zola 1988},{Zola 1991},{Zola 1988, Zola 1991, Zola 1989}. Kinetic studies with radiolabeled material showed that the scFv binds target cells with a dissociation constant of 2.3 x 10-9, which is comparable to the dissociation constant of 4.2 x 10-9 for the parent mAb {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 {Roberts 2018}. The intracellular signaling domain of CD28 provides a costimulatory signal that works in concert with the primary CD3ζ signal to augment T-cell function, including interleukin-2 production {Finney 1998}. Together, these signals stimulate proliferation of the CAR T cells and direct the 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}.

1.2.2. Outcome of Patients Treated With Tecartus in ZUMA-3

Evaluation of the efficacy and safety of Tecartus in adult patients with r/r B-ALL is based on the pivotal Phase 1/2, multicenter, open label study KTE-C19-103, hereafter referred to as ZUMA-3. In ZUMA-3 Phase 2, a total of 71 patients were enrolled (ie leukapheresed) and 55 patients were treated with Tecartus. ZUMA-3 enrollment is complete.

The ZUMA-3 study demonstrated high response rates and durable remissions in subjects with r/r ALL. In the 55 patients treated with Tecartus, the overall complete remission (OCR) rate was 70.9% with a CR rate of 56.4%, which was significantly greater than the prespecified control rate of 40%. Among the 39 patients who achieved a CR or complete remission with incomplete hematologic recovery (CRi), the median time to response was 1.1 months (range: 0.85 to 2.99 months).

As of the 23 July 2021 data cut-off, all treated patients had potential follow-up for ≥ 18 months with a median follow-up time of 20.5 months (95% CI: 0.3, 32.6 months) and a median follow-up time for OS of 24.0 months (95% CI: 23.3, 24.6).

In the primary analysis of ZUMA-3, the rates of any grade Cytokine release syndrome (CRS) and neurologic toxicities in the Phase 2 safety set were 89% and 60%, respectively. The rates of Grade 3 or higher CRS and neurologic toxicities were 24% and 25%, respectively. No subject experienced Grade 5 CRS. One subject experienced a Grade 5 neurologic event of brain herniation. The median time to onset of first CRS symptoms was 5 days (range:1 to 12 days) after infusion of Tecartus. Among the subjects whose CRS symptoms resolved, the median time to resolution of CRS symptoms was 7.5 days (range: 2 to 48 days). The median time to onset of first neurologic toxicities was 9 days (range: 2 to 16 days) after infusion of Tecartus. Among the subjects whose neurologic toxicities resolved, the median time to resolution of neurologic toxicities was7 days (range: 1 to 75 days).

Selected signs and symptoms of CRS and neurologic events are presented in Table 2 and Table 3, respectively.

Table 2. Selected Signs and Symptoms of Cytokine Release Syndrome

Signs and Symptoms of Cytokine Release Syndrome
Pyrexia
Hypotension

Signs and Symptoms of Cytokine Release Syndrome
Hypoxia
Chills
Tachycardia
Headache
Alanine aminotransferase increased
Aspartate aminotransferase increased
Fatigue
Nausea
Diarrhea

Table 3. Selected Signs and Symptoms of Neurologic Events

Signs and Symptoms of Neurologic Events
Encephalopathy
Tremor
Confusional State
Aphasia
Somnolence
Lethargy
Agitation
Disturbance in attention
Memory impairment
Seizure
Delirium
Dysarthrias

Tecartus manufacturing relies on a replication incompetent murine γ-retroviral vector to stably integrate the anti-CD19 CAR transgene into the T-cell genome, thus creating a theoretical risk of oncogenesis via insertional mutagenesis or replication competent retrovirus (RCR). However, numerous clinical studies in patients with hematologic malignancies or solid tumors and in patients infected with human immunodeficiency virus showed no overt genotoxic effects manifested by development of subsequent neoplasms following infusion of T cells that had been transduced with replication incompetent γ-retroviruses encoding a therapeutic TCR or CAR. These findings represent data from 86 unique patients with hematologic malignancies or solid tumors who exhibited clinical benefit and have follow-up ranging from 3 months to 4.8 years. One of these studies (Study NCI 09C0082) is ongoing and has shown no evidence of secondary malignancy over a period of up to 24 months of follow-up in a total of 43 patients with advanced B-cell malignancies.

In the HIV clinical studies, no treatment-related malignancies have been observed among more than 40 patients with HIV who were treated and followed for a period of 1 to 11 years. Notably, Scholler and colleagues have shown that CAR T cells were detected in 98% of post-infusion samples over this period. This analysis represented over 540 patient-years of accumulated follow-up and showed no clinical evidence of viral vector integration mediated toxicity.

Additionally, a comprehensive summary of RCR data derived from patients treated with T cells transduced ex vivo with murine γ-retroviral vectors was performed on 629 follow-up samples obtained 1 month to 8 years after infusion. The data demonstrated a lack of RCR events in patient samples, including samples from HIV-infected patients, across 29 clinical studies. Due to a lack of detectable RCR in patients, the authors further concluded that infectious and replication competent γ-retroviral vector particles used to modify the patient's own T cells are not shed via saliva, urine, or feces into the environment and, therefore, do not represent any risk to organisms present in the environment. Additional vector integration site analyses conducted by the sponsor support the low risk of insertional mutagenesis in patients treated with engineered T-cell products{Chang 2019}.

Taken together, the clinical studies described above suggest that T-cell transformation due to γ–retroviral or lentiviral insertional mutagenesis is an extremely rare event that likely requires the contribution of multiple additional factors beyond the integration site of the viral vector.

The purpose of this study is to analyze and report on the follow-up data for recipients of Tecartus captured in the European Society for Blood and Marrow Transplantation EBMT Registry to address the effectiveness of this product for r/r ALL patients based on OCR rate, OS, DOR and time to next treatment (TTNT) and to describe the long-term safety including incidence rates and severity of Adverse drug reactions(ADRs) and the risk of subsequent neoplasm.

The EBMT is a non-profit organization that was established in 1974 to allow scientists and physicians involved in clinical bone marrow transplantation to share their experiences and develop cooperative studies. More recently, the scope of the organization has broadened to include work in cellular therapy as well. The EBMT has created a specific cell therapy module of its registry and utilizes the infrastructure created for the SCT registry to systematically capture data on all cell therapies. This study will use the data accrued on Tecartus in the EBMT Registry to systematically evaluate information on patients who receive Tecartus.

2. RESEARCH QUESTIONS AND OBJECTIVES

This is a long-term, noninterventional effectiveness and safety study of adult patients [aged 26 years of age and above in the EU , Switzerland and GB)] treated with Tecartus for r/r B-cell precursor ALL.

The study will utilize follow-up data for recipients of Tecartus to determine the effectiveness including OCR rate, OS, and the cause of death and to evaluate the long-term safety including incidence rates and severity of ADRs and the risk of subsequent neoplasm.

Therefore, the study will make secondary use of the data captured in the EBMT Registry, using the infrastructure EBMT created for the SCT registry, to systematically capture information at the time of Tecartus infusion and for up to 15 years of follow-up in the safety cohort. Follow-up for the effectiveness cohort will be stopped once the first 200 eligible patients treated with Tecartus have been documented in the EBMT Registry, and this timepoint is expected to occur approximately 4 years after start of data collection. The effectiveness cohort will also include safety assessments and all patients will be included in the safety cohort.

As this study will make secondary use of data collected under “real-world” conditions, effectiveness and not efficacy will be evaluated. Efficacy can be defined as the performance of an intervention under ideal and controlled circumstances, whereas effectiveness refers to its performance under ”real-world” conditions{Singal 2014}.

The primary objective of this study is:

- To evaluate the effectiveness of Tecartus in terms of OCR rate (complete remission [CR] + complete remission with incomplete hematologic recovery [CRi]).

The secondary objectives of this study are:

- To determine the OS rate and causes of death after administration of Tecartus
- To evaluate DOR
- To evaluate TTNT
- To assess effectiveness (OCR rate, OS, DOR and TTNT) by gender and age and in special populations [patients with prior allo-SCT, patients who receive subsequent allo-SCT and patients treated with Out of Specifications (OOS) product]
- Safety will be evaluated as follows: To evaluate the incidence rate and severity of ADRs in patients treated with Tecartus, including secondary malignancies, CRS, neurologic events, serious infections, prolonged cytopenias, and hypogammaglobulinemia.
- To assess the safety profile by gender and age, and in special populations (patients with prior allo-SCT, patients who receive subsequent allo-SCT and patients treated with OOS product); additional subgroups may also be explored.

- To assess the risk of tumor lysis syndrome (TLS) and aggravated Graft versus Host Disease (GvHD).

The other exploratory objectives of this study are as follows:

- To evaluate pregnancy outcomes in female patients of childbearing potential.

3. RESEARCH METHODS

3.1. Study Design

This study is a long-term, non-interventional effectiveness and safety study planned to evaluate outcomes of adult patients (26 years of age and above in the EU and GB) treated with Tecartus for r/r B-cell precursor ALL, in the post marketing setting making secondary use of data available in the EBMT Registry. The EBMT centers enter data into the EBMT Registry following the EBMT specific procedures and requirements. According to the EBMT monitoring plan the site is responsible for completing the data collection forms within 6 weeks after a patient visit. The preferred and most common option to enter data into the EBMT Registry is direct electronic data entry by a trained and authorized staff member from the center. This option ensures immediate access of the center's data by the EBMT and authorized users. Alternatively, direct data entry by a national registry on behalf of specific centers that submit paper forms to this national registry is possible. Patients' data may be entered up to 1 week prior or anytime following administration of Tecartus infusion. Patients will be followed in the EBMT Registry for both study parts: for the safety cohort for up to 15 years; for the effectiveness cohort until the first 200 eligible patients treated with Tecartus have been documented in the EBMT Registry (which is expected to be approximately 4 years after the start of data collection). Data entry into the EBMT Registry requires signed informed consent by the patient or a legal guardian to allow data to be provided to the EBMT.

3.2. Setting

No treatments, therapy protocols, or procedures are mandated. There is no prescribed visit schedule. Data entered into the EBMT Registry will be obtained from clinical, laboratory, and diagnostic assessments conducted during the course of routine medical practice and available in the patient's medical chart, collected for the primary purpose of patient care. Data will be captured by completion of the EBMT Cellular and Gene Therapy Form for the time points described below (see Section 3.5), using the most current data available.

Data entry into the EBMT Registry will be done by the EBMT centers irrespective of this study according to EBMT guidance documents in their most current versions (eg submitting data to the EBMT).

The EBMT Cellular and Gene Therapy Form was created in close cooperation with the Committee for Human Medicinal Products and other relevant Marketing Authorization Holders. The aim is not to collect all possible information from the medical charts, but to collect the essential information in the EBMT Registry. For safety data, the forms specifically collect data on events of special interest. There is also an option to add other complications/toxicities in the EBMT Registry. The EBMT therefore collects a defined data set as specified in the EBMT Cellular and Gene Therapy Form. The EBMT Cellular and Gene Therapy Form is under the control of the EBMT, and therefore its content may change throughout the course of the study.

Available data within the EBMT Registry will be analyzed for this study at defined time points. In this registry only predefined data of interest will be collected from the medical charts.

Spontaneous ADR reporting independent from this study is the primary source for detecting new safety concerns/signals. New emerging safety concerns and respective data/variables might be added throughout the course of the study on the EBMT Cellular and Gene Therapy Form to support structured data collection of such new relevant data during the study, if agreed to by the EBMT, who owns this form.

3.2.1. Inclusion Criteria

Patients must meet all the following criteria to be eligible for inclusion in this study:

Adult patients (26 years of age and above in the EU and GB) treated with Tecartus for r/r B-cell precursor ALL.

Patients must consent to share clinical data with EBMT.

3.2.2. Exclusion Criteria

Patients who meet *any* of the following criteria will be excluded from the study:

Patients participating in interventional clinical trials at the same time will not be included in this study.

3.3. Variables

This secondary use of data study makes use of the EBMT Registry and is dependent on all needed variables to be collected in the EBMT Cellular and Gene Therapy Form. Furthermore, certain variables may not be generated as part of routine medical practice or because local regulations limit the ability to collect the information.

The EBMT Cellular and Gene Therapy Form specifies the sub-set of data that are transcribed by the centers from the patients' medical charts into the EBMT Registry.

3.3.1. Variables Utilized for Analysis of Primary Objective and Effectiveness Objectives

- OCR and date of remission evaluated.
- Additional treatment and date of treatment received for primary disease (ALL) after Tecartus administration.
- Date and main cause of death, or date of the last day known being alive.

3.3.2. Variables utilized for analysis of Safety Objectives

The EBMT Registry will collect the variables listed and this study will utilize this data for analysis.

- Secondary malignancy is defined as the development of a new malignancy suspected to be possibly related to gene-modified cell therapy (i.e., temporally associated with gene-modified cell therapy and without compelling alternate etiologies). The date of diagnosis, type, and location will be collected.

- CRS is a class effect of CAR T-cell therapies, which may occur at different grades of severity, characterized by fever, rigors, nausea, emesis, headache, hypotension, and pulmonary, hepatic, and renal dysfunction. CRS grade (eg. as in Table 4), system of grading, date of onset, treatment and resolution status will be collected.

- Neurologic toxicity is a class effect of CAR T cell therapies and most commonly includes confusion, delirium, aphasia, obtundation, myoclonus, and seizures. The type, grade, system of grading (Common Terminology of Adverse Events or Immune Effector Cell Associated Neurotoxicity Syndrome score), treatment, date of onset and resolution status of all neurologic toxicities will be collected.

- Prolonged cytopenias are defined as inability to recover the absolute neutrophil count (ANC) and platelets within 30 days after the administration of Tecartus. ANC recovery is defined as neutrophil count $\geq 500/mm^3$ for 3 consecutive values, and platelet recovery is defined as platelet count $\geq 50 \times 10^9/L$ without transfusion support within 7 days. The date of recovery for ANC and platelets will be collected.

- Serious infections are defined as viral, bacterial or fungal infections that require intervention or have led to a negative outcome for the patient (including death) as determined by the treating physician and reported to the EBMT Registry. The type, organism, treatment and date of onset of infection and resolution status will be collected.

- Hypogammaglobulinemia is defined as serum IgG levels below 600 mg/dL. For hypogammaglobulinemia the date of onset, treatment, and resolution status will be collected.

- Grade, date of onset, treatment and resolution of TLS.

- Type, date of onset, and resolution status of aggravated GvHD. For acute GvHD in addition: grade and relationship to cell therapy.

Table 4. Grading of CRS - Modified Lee Grading System

Grade[1]	Sign/Symptom/Intervention
1	Symptoms are not life-threatening and require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)
2	Symptoms require and respond to moderate level of intervention: Oxygen requirement < 40% FiO_2, or Hypotension responsive to intravenous fluid infusion or low dose of one vasopressor, or Grade 2 organ toxicity[2]
3	Symptoms require and respond to aggressive intervention: Oxygen requirement > 40% FiO_2, or Hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity or Grade 4 transaminitis
4	Life-threatening symptoms Requirement for mechanical ventilatory support, or Grade 4 organ toxicity (excluding transaminitis)
5	Death

CRS: Cytokine release syndrome, CTCAE: Common Terminology of Adverse Events, FiO_2: Fraction of inspired oxygen, NCI: National Cancer Institute
1 CRS grading adapted from Lee, et al {Lee 2014}
2 Organ toxicities are defined according to NCI CTCAE.

3.3.3. Variables utilized for analysis of Other Exploratory Objectives

The EBMT Registry will collect data on any pregnancy that occurs after administration of Tecartus and additional information related to the outcome of the pregnancy and the newborn's health, and this study will utilize this data for analysis, where available.

3.3.4. Variables for exposure to Tecartus

- Name and dose level of lymphodepleting chemotherapy received prior to Tecartus infusion.
- Tecartus infusion: date, and whether Tecartus was released at physician's request, because the manufactured product was out of specification.

3.3.5. Variables to Collect for Demographics and Baseline Characteristics

Patient-related variables:

- Age, gender, and country
- Height and weight at the time of Tecartus infusion
- Performance score (Eastern Cooperative Oncology Group or Karnofsky)
- Comorbidities index (Sorror score)

- Active autoimmune, neurologic and hematological disease; infection related complications
- Prior lines of treatment and response
- Disease stage at time of cellular therapy
- Time from diagnosis of the primary disease to cellular therapy
- Prior hematopoietic SCT: allogeneic, donor Human Leukocyte Antigen (HLA) match type (HLA-identical sibling, syngeneic, HLA-matched other relative, HLA-mismatched relative), source of stem cell product (umbilical cord blood, bone marrow, peripheral blood), immunosuppressants (type and duration), prior GvHD
- Prior cellular therapy (other than allogeneic SCT)

3.4. Data Sources

The source data for the EBMT Registry will be the data presented in the patients' medical records. A sub-set of these data from patients' medical records will be transcribed by the centers in the EBMT Registry utilizing the EBMT Cellular and Gene Therapy Form (Appendix 5). The data on patients receiving Tecartus available in the EBMT Registry will be the data source for this study.

The EBMT maintains a registry which encompasses all HSCT procedures for all indications. It also stores immunosuppressive treatments for bone marrow failure syndromes (ie aplastic anemias), cell therapy treatments other than HSCT and donor information pertaining to collection and donor follow up.

All EBMT centers are asked to submit the minimum essential data as recorded through the EBMT Cellular and Gene Therapy Form. Centers are instructed to electronically submit the first registration on the day of treatment (Day 0) or within a week of Day 0. An update should be submitted at 100 days, and 6 months after the date of transplant or cell therapy infusion for nontransplanted patients, or when the patient dies, whichever comes first. Yearly follow-up data should be submitted for all patients from then onwards.

3.5. Data Management

Data will be entered into the EBMT Registry by the centers utilizing the EBMT Cellular and Gene Therapy Form. EBMT will liaise with individual centers and will provide standard training on how to enter the data and how to use the data management system. Trained personnel will enter data directly into the EBMT Registry database, and users will have user accounts with password in order to gain access to the EBMT Registry database. EBMT will cooperate with centers to reduce the amount of missing/erroneous data in the registry.

An imperative need for clear understanding of the secondary nature of the data is appreciated, wherein data are transcribed into the EBMT Registry from the medical record. To fully ensure the secondary categorization of the data is not disrupted, personnel at the centers will be trained

and instructed by the EBMT to enter only information available in the medical record, and to make no inferences outside of this practice.

Data will be collected at the center's standard follow-up time points, including at least time points during the first year at approximately Day 100, 6 and 12 months and then annually thereafter. Expedited reporting of individual case safety reports to EBMT or by EBMT will not occur. Reporting of adverse events (AEs) by centers or clinicians will follow the standard spontaneous reporting system per local regulations and timelines as described in Section 6.

The center that administers Tecartus is responsible for reporting follow-up unless the responsibilities are formally transferred to and accepted by a healthcare provider at another center. Patients who receive a hematopoietic cell transplantation or other cellular therapy or any other treatment for the primary disease after Tecartus will continue to be followed.

EBMT will conduct the study specific analyses and provide overviews to update Kite Inc. regarding the progress of the data entry into the EBMT Registry. Reports will be prepared as described in Section 7.1.

3.6. Study Size

The first 200 eligible patients who have been treated with Tecartus and documented in the EBMT Registry will be included in the effectiveness cohort. It is expected to take approximately 4 years from the start of data collection to document 200 patients in the EBMT Registry.

The sample size of 200 patients will allow an estimate of overall response rate (ORR) and the according 95% confidence interval as tabulated in Table 5:

Table 5. 95% Confidence Interval of ORR by the Assumption of Observed ORR in 200 Patients

Assumed observed ORR based on 200 patients	Lower Limit of 95% CI[b]	Upper Limit of 95% CI[b]
85% (170 out of 200)	**79%**	**90%**
80% (160 out of 200)	74%	85%
75% (150 out of 200)	68%	81%
71% (142 out of 200)[a]	64%	77%
69% (138 out of 200)	62%	75%
65% (130 out of 200)	58%	72%
60% (120 out of 200)	53%	67%

Abbreviations: CI: Confidence Interval, ORR: Overall response rate
a 71% and 69% are the observed ORRs in the ZUMA-3 study {Shah 2021}
b 95% CI is calculated based on Clopper-Pearson exact method

For the safety cohort this study plans to evaluate 300 patients who have been treated with Tecartus and documented in the EBMT Registry within 5 years from study start. In addition to

the further characterization of the immediate and established toxicities of Tecartus, the study will evaluate rare and delayed safety events that occur in patients during 15 years of follow-up. Based on a projection of 300 eligible patients, the available person-years of follow-up are approximated using a piecewise linear survival curve with 2-year survival rate of 55% (assumption based on the primary analysis of ZUMA-3 phase 2 July 2021 data cut) and an assumption of long term 15-year survival rate of 30%, indicating an average person-years of follow-up of 7.14 years. Kite also assumes 10% overall loss to follow-up, resulting in approximately 1927.8 total person-years of follow-up. This number of person-years of follow-up will provide 93%, or 73%, or 58%, or 48%, or 40% likelihood of seeing at least one event of interest, if the true AE rate per person per year of exposure is at least 1:50, or 1:100, or 1:150, or 1:200, or 1:250, respectively.

3.7. Data Analysis

The study will make secondary use of the data available in the EBMT Registry. Analysis of all endpoints for this study will include all patients who satisfy the eligibility criteria, are documented within the EBMT Registry, and are treated with Tecartus.

Categorical variables will be summarized descriptively by number and percentage of patients in each categorical definition and will include 95% CIs. Continuous variables will be summarized descriptively by mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum. This study will evaluate the effect of age, gender, and special populations (patients with prior allogeneic SCT, patients who receive subsequent allo-SCT, patients treated with OOS product) on the effectiveness and safety endpoints using stratified analysis or multivariable regression analyses. Depending on the data, additional baseline characteristics may also be explored.

Patient incidence of endpoint events will be provided. Multivariate Poisson regression analyses will be used to estimate cumulative incidence rates adjusted for follow-up period and specified characteristics (as mentioned in the prior paragraph) to estimate their prognostic effect on the outcome.

Kaplan Meier curves will be used to illustrate all time-to-event data. Competing risk analysis method will be used for the analysis of time to onset and duration of endpoint events. TTNT and the cumulative incidence at specified time points will be provided. Cox-proportional hazard models will be used to model multivariate time-to-event data adjusted for specified characteristics (as mentioned in the prior paragraph) to estimate their prognostic effect on the outcome. For the effectiveness cohort the analysis of the effectiveness endpoints will be conducted when effectiveness data from approximately 200 eligible patients are documented.

3.7.1. Primary Analysis (Effectiveness Endpoints)

3.7.1.1. Analysis of Primary Endpoint

OCR: OCR, defined as the incidence of (CR) + CRi, will be calculated. The 95% confidence intervals will be provided for OCR using exact binomial methods.

3.7.1.2. Effectiveness Endpoints

- OS is the time from the date of the first Tecartus infusion to the date of death due to any reason. All patients will be followed up for survival information regardless of whether they received additional treatment post-infusion. Patients who are alive at last contact will be censored at that time, but no censoring will be done for additional treatment. OS will be summarized using the Kaplan-Meier estimate. The median OS along with 95% CIs will be presented if appropriate. Causes of death will also be reported.

- DOR is defined as the time from the date of the first documented remission (CR or CRi) to the date of the first documented relapse or death due to primary disease, whichever happens first. DOR is determined only among patients who achieve a CR after the first infusion of Tecartus. The cumulative incidence of DOR and corresponding 95% CIs will be estimated using a competing risk analysis method, with deaths due to reasons other than primary disease considered as a competing risk.

- TTNT of the primary disease is defined as time from Tecartus infusion to next treatment of the primary disease or death due to relapse of the primary disease. Non-primary disease related mortality will be taken as a competing risk. The cumulative incidence of TTNT and 95% CI will be estimated using competing risk analysis method, where death without relapse or without subsequent treatment of primary disease is considered as a competing risk.

- Patients' missing data for effectiveness variables will be treated as non-responders. In case the patient's data will be excluded, clarification for exclusion will be provided.

3.7.2. Secondary Analyses (Safety Endpoints)

- Secondary malignancy: The overall incidence of secondary malignancies and secondary malignancy by type and location will be summarized using frequencies and percentages, as well as follow-up adjusted rates. Cumulative incidence curve of time to onset of secondary malignancy will be shown out to 15 years, treating death prior to secondary malignancy as a competing event. Estimates and 95% CIs for the cumulative incidence of secondary malignancy will be provided at 1, 2, 5, 10, and 15 years.

- CRS: The overall incidence and grade of CRS will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of CRS and 95% CIs will also be estimated using competing risk analysis method, with death before experiencing CRS treated as a competing event for the onset of CRS up through 30 days after Tecartus infusion. Cumulative incidence curve of time to onset of CRS will also be provided. Management and resolution of CRS will also be described.

- Neurologic events: The incidence and grade of neurologic events, both overall and by type, will be described using frequencies and percentages, as well as follow-up adjusted rates. The incidence of neurologic events and 95% CIs will also be estimated using competing risk analysis method, with death before experiencing neurologic events treated as a competing event for the onset of neurologic events up through 90 days after Tecartus infusion. Cumulative incidence curve of time to onset of neurologic events will also be provided. Treatment and resolution of neurologic toxicities will be described.

- Prolonged cytopenias: The proportion of patients who fail to recover ANC and platelet counts, as previously specified, by Day 30 after the administration of Tecartus will be described along with 95% CIs using exact binomial methods. Time to event analysis for ANC and platelets recovery will be carried out by completing risk analysis treating death without recovery of ANC or platelets as competing risk. The point estimate and 95% CIs of cumulative incidence will be reported accordingly.

- Serious infections: The incidence of serious infections, type and organism will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of serious infections after Tecartus infusion and 95% CIs will be estimated using competing risk analysis method, with death before experiencing serious infections treated as a competing event. Cumulative incidence curve of time to serious infections will also be provided. Resolution of serious infections will be described.

- Hypogammaglobulinemia: The incidence of hypogammaglobulinemia will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of hypogammaglobulinemia after Tecartus infusion and 95% CIs will be estimated using competing risk analysis method, with death before experiencing hypogammaglobulinemia treated as a competing event. Cumulative incidence curve of time to hypogammaglobulinemia will also be provided. Use of replacement Ig therapy will also be described as part of this endpoint.

- TLS: The overall incidence and grade of TLS will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of TLS after Tecartus infusion and 95% CIs will be estimated using competing risk analysis. Cumulative incidence curve of time to onset of TLS will also be provided. Resolution of TLS will be described.

- Aggravated GvHD: The incidence of GvHD, both overall and by acute and chronic type, will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of GvHD after Tecartus infusion and 95% CIs will be estimated using competing risk analysis. Cumulative incidence curve of time to onset of aggravated GvHD will also be provided. The severity/grade and relationship to Tecartus for acute GvHD will also be summarized.

- Safety endpoints on subgroups by gender, age, and in special populations (patients who receive a subsequent allo-SCT, patients treated with OOS product), and additional subgroups may also be explored.

3.7.3. Other Analyses

Pregnancy and pregnancy outcome: Both the proportion of women who become pregnant and the pregnancy outcome and the newborn's health will be described and summarized as part of this outcome, where available.

AEs in general will be summarized for their incidences descriptively.

3.8. Quality Control

The data collected will be entered in the EBMT database according to standard operating procedures, work instructions, manuals and guidelines that are in place and maintained by EBMT.

At a registry level EBMT has built in more than 4,000 control triggers, which promote consistency of the data. In addition, EBMT personnel and registry users can run data quality reports, which predominantly focus on missing data. For all studies (both retrospective and prospective) based on registry data, additional data cleaning efforts, including the analyses of outliers, additional data requests and if needed statistic adjustments for missing data, are performed.

Apart from remote monitoring activities, on-site monitoring of data for 10% of the included Tecartus patients will be performed by the EBMT. Centers will be selected for on-site monitoring based on a risk-based approach using quality indicators as described in the monitoring plan.

Additional quality control measures supported by EBMT include:

- Automatic data validation checks verify the accuracy and internal consistency of entries in the database at the point of entry.

- Data quality control reports can be run by users (or by registry personnel) to check for missing, inconsistent or incorrect data.

- Follow-up requests on missing or incorrect data are issued by the registry/Study Office; this also applies, if yearly follow-up data were not submitted for a patient during the up to 15 year follow-up period.

- Education and training sessions (face to face and on-line) are available for data entry staff.

Remote manual data quality review is performed in accordance with the study data quality and monitoring documents. In addition, monitors will engage centers with regard to data quality and

completeness via telephone calls and may perform onsite visits, as documented in the EBMT monitoring plan.

3.9. Limitations of the Research Methods

The EBMT Registry allows patient data entry any time after Tecartus infusion; therefore, this study has the characteristic disadvantages of retrospective studies, and these include information bias, history bias and recall bias. However, there will be an effort to encourage patient documentation in the EBMT Registry as promptly as possible to capture data continuously. The EBMT monitoring plan further states that the site is responsible for completing the data collection forms within 6 weeks after a patient visit.

Information bias can be prevented by using standard measurement instruments, such as the electronic data collection form and appropriate training of personnel entering the data. Appropriate training of personnel entering data is also important to avoid missing values when checking the patients' medical records.

3.10. Other Aspects

This study will be conducted according to the Good Pharmacoepidemiology Practice and in line with the relevant Modules of the Heads of Medicines Agencies Good Pharmacovigilance Practices (GVP).

No patient's treatment will be dictated by the protocol of this long-term observational study or by EBMT, or Kite. Consequently, continuing or discontinuing this study will not impact patient care. Therefore, identification of adverse effects of Tecartus will not constitute sufficient reason to terminate the study. However, early termination of the study will be considered if:

- Sufficient information is accumulated to meet the scientific objectives of the study
- The feasibility of collecting sufficient information is reduced to unacceptable levels because of low exposure rates, extremely slow patient accrual, or loss of the ability to follow-up

In case such conditions are met, any consideration for termination of the study will be discussed and agreed on with the European Medicines Agency (EMA) beforehand.

4. PROTECTION OF HUMAN SUBJECTS

Because this is a non-interventional study with no pre-specified interventions and no interaction with patients, no potential physical or psychological risks to patients exist. This study will make secondary use of data collected within the EBMT Registry to capture information about Tecartus.

EBMT will use standard processes for ensuring the protection of human subjects for patients whose cellular therapy data are reported to the EBMT Registry. Participating centers are responsible for obtaining informed consent for patient data entry into the EBMT Registry, registering patients, and submitting baseline and follow-up data on participating patients into the EBMT Registry following EBMT's procedures and requirements.

There is no potential benefit to those who agree to have their data entered into the EBMT Registry. All benefits of long-term follow-up data collection will assist in understanding late effects that occur after treatment with CAR T cells, and thus may benefit future patients. The only risk to patients is the risk of loss of privacy and confidentiality. This is a well-mitigated risk with respect to the potential benefit of knowledge gained through these research studies.

4.1. Institutional Review Board or Independent Ethics Committee Review and Approval

The study will be conducted in accordance with the EMA Guideline on GVP, following the requirements for studies making secondary use of data, and including the archiving of essential documents. The study will further be conducted in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), by enclosing the ENCePP Checklist in the submission and registering the study in the European Union electronic Register of Post Authorisation Studies (EU PAS) Registry.

No Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) review is required for this secondary analysis of existing data if there is no obligation in the local regulations.

4.2. Confidentiality

All data evaluated for this study will be collected in an EBMT data collection form with a unique identifier for each patient by each participating center. The patient identifiers will be removed and the data will contain no patient identifiable fields when analyzed data is shared with Kite by the EBMT.

4.3. Informed Consent

No specific informed consent will be obtained to participate in this study, as this study will involve secondary analysis of data already existing in the EBMT Registry. According to established practices of the EBMT and country requirements, at each of the centers an informed consent document will be obtained from each participating patient and maintained at the center.

With this informed consent document patients will provide consenting for input of their data into the EBMT Registry.

5. RESPONSIBILITY AND STUDY CONDUCT

5.1. Protocol Modifications

Not Applicable.

5.2. Study Files and Retention of Records

For studies based on use of secondary data, all analytical datasets will be maintained per records retention schedule and local regulations.

5.3. Access to Information for Audit and Inspections

Representatives of regulatory authorities or of Kite may conduct inspections or audits of the study. If the EBMT is notified of an inspection by a regulatory authority, the EBMT must notify Kite immediately. The EBMT agrees to provide to representatives of a regulatory agency or Kite access to records, facilities, and personnel for the effective conduct of any inspection or audit.

5.4. Protocol Compliance

Not applicable.

6. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

The operational model for this PAS protocol qualifies as non-interventional research with a design based on secondary use of data (ie utilizing data from patients' medical records that were previously collected for another purpose and included into the EBMT Registry data set, and where the AEs have already occurred and will not be reported in expedited manner) as outlined in GVP Module VI. According to this guidance, reporting of safety information in the form of individual case safety reports is not required and all AE and safety data are only required to be recorded and summarized in the interim safety analysis and in the final study report. All AEs will be summarized in aggregate during all reporting efforts, including in the interim and final study reports.

Reporting of individual AE and adverse reactions will follow the standard spontaneous reporting system per local regulations and timelines. The centers will report any suspected adverse reactions directly to Kite or respective health authorities. The Summary of Product Characteristics and packaging materials provide respective details and contact information. Kite further provides clear guidance to Health care professionals (HCPs) in the additional Risk Minimization Measures of the need and importance of spontaneously reporting and that this is not substituted by reporting into the EBMT Registry.

Kite is responsible for analyzing spontaneous reports of all safety information received independently from this study and for reporting to regulatory agencies as determined by country-specific legislation or regulations.

6.1. Definitions

6.1.1. AEs

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and should be reported.

- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)

- Any medical condition or clinically significant laboratory abnormality with an onset date before treatment initiation. These are preexisting and should be documented on the medical history CRF (if applicable).

6.1.2. Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) for this study are considered to be events in the focus of the safety objectives: secondary malignancies, CRS, neurologic events, serious infections, prolonged cytopenia, hypogammaglobulinemia, TLS and aggravated GvHD.

6.1.3. ADRs

An ADR is defined as an untoward medical occurrence (unintended or noxious response) considered causally related to an investigational or approved medicinal product at any dose administered. Adverse reactions may arise from medication errors, uses outside what is foreseen in the protocol or prescribing information (off-label use), misuse and abuse of the product, overdose, or occupational exposure.

6.1.4. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- A life-threatening situation (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

6.1.5. Serious Adverse Drug Reaction

A serious adverse drug reaction (SADR) is defined as any SAE that is considered causally related to the medicinal product at any dose administered.

6.1.6. Special Situations Reports

This study has an exploratory objective to investigate pregnancy outcomes in female patients of childbearing potential. Other special situation reports (SSRs) are not within the objectives of the study, but if reported spontaneously, Kite will accept these reports and handle them as appropriate.

SSRs include reports of abuse, drug interactions, counterfeit or falsified medicine, exposure via breastfeeding, lack of effect, medication error, misuse, occupational exposure, off-label use, overdose, pregnancy, transmission of infectious agents via the product, and unexpected benefit. Definitions and examples are provided below:

- Abuse: Persistent or sporadic intentional excessive use of a medicinal product by a patient.
- Drug interactions: Any reports of drug/drug, drug/food, or drug/device interactions.
- Counterfeit or falsified medicine: Any medicinal product with a false representation of a) its identity, including its packaging and labeling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients; b) its source, or c) its history.
- Exposure via breastfeeding: Reports of any exposure to a medicinal product during breastfeeding.
- Lack of effect: A report of a situation where there is apparent failure of the medicinal product or medical technology to bring about the intended beneficial effect on individuals in a defined population with a given medical problem, under ideal conditions of use.
- Medication error: Any unintentional error in the prescribing, dispensing, preparation for administration or administration of a medicinal product while the medication is in the control of a healthcare professional, patient, or consumer.
- Misuse: Use of a medicinal product that is intentional and inappropriate not in accordance with its authorized product information.
- Occupational exposure: Exposure to a medicinal product as a result of one's professional or non-professional occupation.
- Off-label use: Where a medicinal product is intentionally used by an HCP for a medical purpose not in accordance with the authorized product information with respect to indication, dose, route of administration, or patient population (e.g., the elderly).
- Overdose: An accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose in the product labelling.

- Pregnancy reports (maternal pregnancy and partner pregnancy; refer to Section 6.2.4 for study specific reporting requirements, if any): Reports of pregnancy following maternal or paternal exposure to the product.

- Unexpected benefits: An unintended therapeutic effect where the results are judged to be desirable and beneficial.

- Transmission of infectious agents via the product: Any suspected transmission of an infected agent through a medicinal product.

6.2. Investigator Instructions for Collecting and Reporting Safety Information to Kite

6.2.1. Safety Information to be Collected

Not Applicable.

6.2.2. Timelines for Reporting Safety Information

Not applicable.

6.2.3. Process for Reporting to Kite

Not applicable.

6.2.4. Instructions for Reporting Pregnancies

Not applicable.

6.3. Kite Reporting Requirements to Regulatory Authorities

Kite is responsible for analyzing reports of all safety information received independently from this study and reporting to regulatory agencies as determined by country-specific legislation or regulations.

6.4. Clinical Laboratory Abnormalities

Not applicable.

6.5. Assessment of Causality for Study Drugs

Where applicable, the investigator or qualified sub-investigator is responsible for assessing the causal relationship to drug therapy for each event and using clinical judgment and the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the drug. For SAEs, an alternative causality must be provided (e.g., preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes:** There is a reasonable possibility that the event may have been caused by the medicinal product (and thus reported as an ADR or SADR).

It should be emphasized that ineffective treatment should not be considered as causally related in the context of reporting safety information.

7. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

7.1. Study Report and Publications

7.1.1. Safety Data Reports

The safety data reports will contain the following information, as available:

- Patient enrollment in registry
- Baseline characteristics
- Aggregate numbers of reported fatal AEs
- Aggregate numbers of all reported AEs
- Review of events considered AESIs via the safety objectives of this study: secondary malignancies, CRS, neurologic events, serious infections, prolonged cytopenia, hypogammaglobulinemia, TLS and aggravated GvHD
- If reported, review of other events outside of the AESIs
- Summary and conclusions

Particular attention will be paid to AESIs, which are considered to be the events which are the focus of the safety objectives (please see below and in Section 6.1.2).

7.1.2. Annual Reports

For the effectiveness cohort annual reports will be prepared for the first 3 years, in which an analysis of treated patients for the primary and the effectiveness endpoints will be included. For the safety cohort annual reports will be prepared for the first 5 years and then every 2 years thereafter, in which an analysis of treated patients for the safety endpoints will be included. The EBMT Cellular and Gene Therapy Form is under the control of the EBMT and its content can change throughout the course of the study (see section 3.2).

Based upon the approved reports, Kite will submit information to regulatory agencies in accordance with any agreements/commitments.

7.1.3. Final Report

Following the final data analysis, Kite and EBMT will cooperate to prepare an appropriate final report, which will be submitted to the Regulatory authorities as applicable by Kite as the study sponsor.

7.1.4. Publications, Conference Abstracts, and Manuscripts

All proposed publications and conference presentations arising from the study will be reviewed by Kite and EBMT representatives prior to submission. Both EBMT and Kite will share responsibilities in the development of the statistical analysis plan, data analysis, abstracts and

manuscripts. The EBMT investigators and Kite staff may share authorship. The study contract between EBMT and Kite will outline the requirements for publication.

Kite shall communicate the final manuscript to the EMA and the competent authorities of the Member States in which the product is authorized within 2 weeks after first acceptance for publication. Authorship of study manuscripts and presentations at scientific conferences will follow the guidelines established by the International Committee of Medical Journal Editors (https://www.icmje.org/).

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9. APPENDICES

Appendix 1. List of Stand-Alone Documents

Responsible Parties

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
Marketing Authorization Holder	Kite Gilead Sciences International Ltd Clare Coombs Sr Manager, Regulatory Affairs Flowers Building Granta Park, Abington Cambridge, CB21 6GT UK	Phone: +44 1223 897586 Email: clare.coombs1@gilead.com
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Biostatistics	Hailin Wang Senior Manager, Biostatistics Kite Pharma, Inc. 333 Lakeside Drive Foster City, CA 27717-0530 USA	Phone: +1 XXXXX Email: hwang14@kitepharma.com
Clinical Operations	Erkan Su Clinical Trial Manager Gilead Sciences Europe 2 Roundwood Avenue Stockley Park Uxbridge, UB11 1AF United Kingdom	Phone: ++44 20 8587 2372 Email: erkan.su1@gilead.com
Pharmacovigilance	Global Patient Safety (GLPS) Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 27717-0530 USA	Phone: +1 800 445 3235 Fax: +1 650 522 5477 Email: Safety_fc@gilead.com
European Union Qualified Person for Pharmacovigilance (EU QPPV)	Anne-Ruth van Troostenburg de Bruyn Vice President, GLPS Gilead Sciences GmbH Fraunhoferstr. 17 82152 Martinsried Germany	Phone: +49 (0) 89 899 890 181 Email: euqppv@gilead.com

Appendix 2. ENCePP Checklist for Study Protocols

Study title:
LONG-TERM, NON-INTERVENTIONAL STUDY OF THE TREATMENT BY TECARTUS OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY (R/R) B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

EU PAS Register® number: tbd
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	4, 7
2.1.2 The objective(s) of the study?	☒	☐	☐	4, 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	4, 9
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	4, 9
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.6
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	9
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	4, 9
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	4, 9
	4.2.2 Age and sex	☐	☒	☐	
	4.2.3 Country of origin	☐	☒	☐	
	4.2.4 Disease/indication	☒	☐	☐	4, 9
	4.2.5 Duration of follow-up	☒	☐	☐	4, 9
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	4, 9

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	9.7
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	9.7
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	4, 8, 9
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	4, 9
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	4, 9
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☒	☐	9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	4, 9

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	4, 9
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	4, 9
9.1.3 Covariates and other characteristics?	☒	☐	☐	4, 9
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	4, 9

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	4, 9
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	4, 9
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	9.7
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9
9.3.3 Covariates and other characteristics?	☐	☒	☐	9
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	10

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	4, 9
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	4, 9
10.3 Are descriptive analyses included?	☒	☐	☐	4, 9
10.4 Are stratified analyses included?	☐	☒	☐	9
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	9
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	9

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☒	☐	
12.1.2 Information bias?	☒	☐	☐	9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	9

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☐	☐	☒	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Alexandros Sagkriotis

Date: 08/December/2022

Signature: _____

ENCePP Checklist for Study Protocols_Appendix 2

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
Alexandros Sagkriotis	Epidemiology eSigned	08-Dec-2022 14:42:54

Appendix 3. Kite Signature Page

Kite Pharma Inc.

2400 BROADWAY SANTA MONICA, CA 90404 USA

LONG-TERM, NON-INTERVENTIONAL STUDY OF THE TREATMENT BY TECARTUS OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY (R/R) B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

ORIGINAL, 08 DECEMBER 2022

This protocol has been approved by Kite Pharma Inc. The following signatures document this approval.

Alexandros Sagkriotis	
Study Director (Printed) Author	Signature
Date	

Dr. Anne-Ruth van Troostenburg de Bruyn	
Kite EU QPPV (Printed)	Signature
Date	

Kite Signature Page_Appendix 3

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
Alexandros Sagkriotis	Epidemiology eSigned	08-Dec-2022 14:42:30
Anna Vantroostenburg	QPPV eSigned	08-Dec-2022 16:50:24

Appendix 4. Reference Safety Information

Current version of the European Union Summary of product characteristics for Tecartus®.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Tecartus (autologous anti-CD19-transduced CD3+ cells) is a gene therapy medicinal product containing autologous T cells genetically modified *ex vivo* using a retroviral vector encoding an anti-CD19 chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 co-stimulatory domain and CD3-zeta signalling domain.

2.2 Qualitative and quantitative composition

Each patient specific single infusion bag contains a dispersion of anti-CD19 CAR T cells in approximately 68 mL for 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.

Excipient(s) with known effect

This medicinal product contains 300 mg sodium.
Each dose contains 0.05 mL of dimethyl sulfoxide (DMSO) per mL of Tecartus.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion.

A clear to opaque, white to red dispersion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tecartus is indicated 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.

4.2 Posology and method of administration

Tecartus must be administered in a qualified treatment centre by a physician with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Tecartus. At least 1 dose of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion. The qualified treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose.

Patients are expected to enrol in a registry and will be followed in the registry in order to better understand the long-term safety and efficacy of Tecartus.

Posology

Tecartus is intended for autologous use only (see section 4.4).

A single dose of Tecartus contains 2×10^6 CAR-positive viable T cells per kg of body weight (range: 1×10^6–2×10^6 cells/kg), or maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above in approximately 68 mL dispersion in an infusion bag.

Tecartus is recommended to be infused 3 to 14 days after completion of the lymphodepleting chemotherapy. The availability of the treatment must be confirmed prior to starting the lymphodepleting regimen.

Pre-treatment (lymphodepleting chemotherapy)

- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m² and fludarabine 30 mg/m² should be administered intravenously on the 5th, 4th, and 3rd day before infusion of Tecartus.

Pre-medication

- To minimise potential acute infusion reactions, it is recommended that patients be pre-medicated with paracetamol 500 to 1,000 mg given orally and diphenhydramine 12.5 to 25 mg intravenous or oral (or equivalent) approximately 1 hour prior to infusion.
- Prophylactic use of systemic corticosteroids is not recommended (see section 4.5).

Monitoring after infusion

- Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurologic events.
- After the first 10 days following the infusion, the patient should be monitored at the physician's discretion.
- Patients should be instructed to remain within proximity (within 2 hours of travel) of a qualified treatment centre for at least 4 weeks following infusion.

Special populations

Elderly

No dose adjustment is required in patients ≥65 years of age.

Patients seropositive for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV)

There is no experience with manufacturing Tecartus for patients with a positive test for HIV, active HBV, or active HCV infection. Therefore, the benefit/risk has not yet been established in this population.

Paediatric population

The safety and efficacy of Tecartus in children and adolescents aged less than 18 years have not yet been established. No data are available.

Method of administration

Tecartus is for intravenous use only.

Tecartus must not be irradiated. Do NOT use a leukodepleting filter.

Precautions to be taken before handling or administering the medicinal product
This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Tecartus should take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases (see section 6.6).

Preparation for infusion
- Verify that the patient's identity (ID) matches the patient identifiers on the Tecartus metal cassette.
- The Tecartus infusion bag must not be removed from the metal cassette if the information on the patient-specific label does not match the intended patient.
- Once the patient ID is confirmed, remove the infusion bag from the metal cassette.
- Check that the patient information on the metal cassette label matches that on the bag label.
- Inspect the infusion bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines for handling of waste of human-derived material (or immediately contact Kite).
- Place the infusion bag inside a second bag.
- Thaw Tecartus at approximately 37 °C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Tecartus should not be washed, spun down, and/or re-suspended in new media prior to infusion. Thawing should take approximately 3 to 5 minutes.
- Once thawed, Tecartus is stable at room temperature (20 °C – 25 °C) for up to 3 hours. However, Tecartus infusion should begin within 30 minutes of thaw completion.

Administration
- For autologous single use only.
- Tocilizumab and emergency equipment should be available prior to infusion and during the monitoring period.
- A leukodepleting filter must not be used.
- Central venous access is recommended for the administration.
- Verify the patient ID again to match the patient identifiers on the Tecartus bag.
- Prime the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) prior to infusion.
- Infuse the entire content of the Tecartus bag within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the bag during infusion to prevent cell clumping.
- After the entire content of the bag is infused, rinse the tubing at the same infusion rate with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) to ensure all the treatment is delivered.

For instructions on the handling, accidental exposure to and disposal of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Contraindications of the lymphodepleting chemotherapy must be considered.

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient should be kept for a period of 30 years.

General

Warnings and precautions of lymphodepleting chemotherapy must be considered.

Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurologic events. After the first 10 days following infusion, the patient should be monitored at the physician's discretion.

Counsel patients to remain within the proximity of a qualified treatment centre for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS or neurological adverse reactions occur. Monitoring of vital signs and organ functions should be considered depending on the severity of the reaction.

Reasons to delay treatment

Due to the risks associated with Tecartus treatment, infusion should be delayed if a patient has any of the following conditions:

- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions, or hypotension) including from preceding chemotherapies.
- Active uncontrolled infection or inflammatory disease.
- Active graft-versus-host disease (GvHD).

In some cases, the treatment may be delayed after administration of the lymphodepleting chemotherapy regimen. If the infusion is delayed for more than 2 weeks after the patient has received the lymphodepleting chemotherapy, lymphodepleting chemotherapy regimen should be administered again (see section 4.2)

Serological testing

Screening for HBV, HCV, and HIV should be performed before collection of cells for manufacturing of Tecartus (see section 4.2).

Blood, organ, tissue and cell donation

Patients treated with Tecartus should not donate blood, organs, tissues, or cells for transplantation.

Active central nervous system (CNS) lymphoma

There is no experience of use of this medicinal product in patients with active CNS lymphoma defined as detectable cerebrospinal fluid malignant cells or brain metastases confirmed by imaging. Therefore, the benefit/risk of Tecartus has not been established in this population.

Concomitant disease

Patients with a history of or active CNS disorder or inadequate renal, hepatic, pulmonary, or cardiac function were excluded from the study. These patients are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

Cytokine release syndrome

Nearly all patients experienced some degree of CRS. Severe CRS, which can be life-threatening, was very commonly observed with Tecartus with a median time to onset of 3 days (range: 1 to 13 days). Patients should be closely monitored for signs or symptoms of these events, such as high fever, hypotension, hypoxia, chills, tachycardia and headache (see section 4.8). CRS should be managed at the physician's discretion, based on the patient's clinical presentation and according to the CRS management algorithm provided in Table 1.

Diagnosis of CRS requires excluding alternate causes of systemic inflammatory response, including infection.

Management of cytokine release syndrome associated with Tecartus
At least 1 dose per patient of tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, must be on site and available for administration prior to Tecartus infusion. The qualified treatment centre should have access to an additional dose of tocilizumab within 8 hours of each previous dose.

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, as summarised in Table 1. Patients who experience Grade 2 or higher CRS (e.g. hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should 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.

CRS has been known to be associated with end organ dysfunction (e.g., hepatic, renal, cardiac, and pulmonary). In addition, worsening of underlying organ pathologies can occur in the setting of CRS. Patients with medically significant cardiac dysfunction should be managed by standards of critical care and measures such as echocardiography should be considered. In some cases, macrophage activation syndrome (MAS) and haemophagocytic lymphohistiocytosis (HLH) may occur in the setting of CRS.

Evaluation for haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) should be considered in patients with severe or unresponsive CRS.

Tecartus continues to expand and persist following administration of tocilizumab and corticosteroids. Tumour necrosis factor (TNF) antagonists are not recommended for management of Tecartus-associated CRS.

Table 1 CRS grading and management guidance

CRS Grade *(a)*	**Tocilizumab**	**Corticosteroids**
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	If not improving after 24 hours, administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg).	N/A

CRS Grade *(a)*	Tocilizumab	Corticosteroids
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO_2 or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity *(b)*.	Administer tocilizumab *(c)* 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24 hour period; maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS, or if no response to second or subsequent doses of tocilizumab, consider alternative measures for treatment of CRS. If improving, discontinue tocilizumab.	If no improvement within 24 hours after starting tocilizumab, manage as per Grade 3. If improving, taper corticosteroids, and manage as Grade 1.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours) until Grade 1, then taper corticosteroids. If improving, manage as Grade 2. If not improving, manage as Grade 4.
Grade 4 Life-threatening symptoms. Requirements for ventilator support or continuous veno-venous haemodialysis or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer methylprednisolone 1000 mg intravenously per day for 3 days. If improving, taper corticosteroids, and manage as Grade 3. If not improving, consider alternate immunosuppressants.

N/A = not available/not applicable
(a) Lee et al 2014.
(b) Refer to Table 2 for management of neurologic adverse reactions.
(c) Refer to tocilizumab summary of product characteristics for details.

Neurologic adverse reactions

Severe neurologic adverse reactions (encephalopathy, confusional state or delirium, decreased level of consciousness, seizures, aphasia), which could be life-threatening, were very commonly observed in patients treated with Tecartus with a median time to onset of 8 days (range: 1 to 262 days) (see section 4.8).

Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive-care supportive therapy for severe or life-threatening neurologic toxicities. Non-sedating, anti-seizure medicines should 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 Table 2.

Table 2 Neurologic adverse reaction grading and management guidance

Grading assessment	Concurrent CRS	No concurrent CRS
Grade 2	Administer tocilizumab as per Table 1 for management Grade 2 CRS. If not improving within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less, then taper corticosteroids. If improving, discontinue tocilizumab. If still not improving, manage as Grade 3.	Administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less. If improving, taper corticosteroids
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 3	Administer tocilizumab as per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids. If improving, discontinue tocilizumab and manage as Grade 2. If still not improving, manage as Grade 4.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids. If not improving, manage as Grade 4.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab as per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days. If improving, then manage as Grade 3. If not improving, consider alternate immunosuppressants.	Administer methylprednisolone 1000 mg intravenously per day for 3 days. If improving, then manage as Grade 3. If not improving, consider alternate immunosuppressants.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

Infections and febrile neutropenia

Severe infections, which could be life-threatening, were very commonly observed with Tecartus (see section 4.8).

Patients should be monitored for signs and symptoms of infection before, during and after infusion and treated appropriately. Prophylactic antibiotics should be administered according to standard institutional guidelines.

Febrile neutropenia has been observed in patients after Tecartus infusion (see section 4.8) and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

In immunosuppressed patients, life-threatening and fatal opportunistic infections including disseminated fungal infections and viral reactivation (e.g., HHV-6 and progressive multifocal leukoencephalopathy) have been reported. The possibility of these infections should be considered in patients with neurologic events and appropriate diagnostic evaluations should be performed.

Viral reactivation

Viral reactivation, e.g. Hepatitis B virus (HBV) reactivation, can occur in patients treated with medicinal products directed against B cells and could result in fulminant hepatitis, hepatic failure, and death.

Prolonged cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Tecartus infusion and should be managed according to standard guidelines. Grade 3 or higher prolonged cytopenias following Tecartus infusion occurred very commonly and included thrombocytopenia, neutropenia, and anaemia (see section 4.8). Patient blood counts should be monitored after Tecartus infusion.

Hypogammaglobulinaemia

B-cell aplasia leading to hypogammaglobulinaemia can occur in patients receiving treatment with Tecartus. Hypogammaglobulinaemia was very commonly observed in patients treated with Tecartus (see section 4.8). Hypogammaglobulinaemia predisposes patients to have infections. Immunoglobulin levels should be monitored after treatment with Tecartus and managed using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement in case of recurrent infections and should be taken according standard guidelines.

Hypersensitivity reactions

Serious hypersensitivity reactions including anaphylaxis, may occur due to DMSO or residual gentamicin in Tecartus.

Secondary malignancies

Patients treated with Tecartus may develop secondary malignancies. Patients should be monitored life-long for secondary malignancies. In the event that a secondary malignancy occurs, the company should be contacted to obtain instructions on patient samples to collect for testing.

Tumour lysis syndrome (TLS)

TLS, which may be severe, has occasionally been observed. To minimise risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to Tecartus infusion. Signs and symptoms of TLS should be monitored, and events managed according to standard guidelines.

Prior stem cell transplantation (GvHD)

It is not recommended that patients who underwent an allogeneic stem cell transplant and suffer from active acute or chronic GvHD receive treatment because of the potential risk of Tecartus worsening GvHD.

Prior treatment with anti-CD19 therapy

Tecartus is not recommended if the patient has relapsed with CD19-negative disease after prior anti-CD19 therapy.

Sodium content

This medicinal product contains 300 mg sodium per infusion, equivalent to 15% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Prophylactic use of systemic corticosteroids may interfere with the activity of Tecartus. Prophylactic use of systemic corticosteroids is therefore not recommended before infusion (see section 4.2).

Administration of corticosteroids as per the toxicity management guidelines does not impact the expansion and persistence of CAR T cells.

Live vaccines

The safety of immunisation with live viral vaccines during or following Tecartus treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Tecartus treatment, and until immune recovery following treatment.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

The pregnancy status of women of childbearing potential must be verified before starting Tecartus treatment.

See the prescribing information for lymphodepleting chemotherapy for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with Tecartus.

Pregnancy

There are no available data with Tecartus use in pregnant women. No reproductive and developmental toxicity animal studies have been conducted with Tecartus to assess whether it can cause foetal harm when administered to a pregnant woman (see section 5.3).

It is not known if Tecartus has the potential to be transferred to the foetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause foetal toxicity, including B-cell lymphocytopenia. Therefore, Tecartus is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised on the potential risks to the foetus. Pregnancy after Tecartus therapy should be discussed with the treating physician.

Assessment of immunoglobulin levels and B-cells in newborn infants of mothers treated with Tecartus should be considered.

Breast-feeding

It is unknown whether Tecartus is excreted in human milk or transferred to the breast-feeding child. Breast-feeding women should be advised of the potential risk to the breast-fed child.

Fertility

No clinical data on the effect of Tecartus on fertility are available. Effects on male and female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

Tecartus has major influence on the ability to drive and use machines.

Due to the potential for neurologic events, including altered mental status or seizures, patients should not drive or operate heavy or potentially dangerous machines until at least 8 weeks after infusion or until resolution of neurologic adverse reactions.

4.8 Undesirable effects

Summary of the safety profile

The safety data described in this section reflect exposure to Tecartus in ZUMA-2, a Phase 2 study in which a total of 82 patients with relapsed/refractory MCL received a single dose of CAR-positive viable T cells (2×10^6 or 0.5×10^6 anti-CD19 CAR T cells/kg) based on a recommended dose which was weight-based.

The most significant and frequently occurring adverse reactions were cytokine release syndrome (91%), infections (56%) and encephalopathy (51%).

Serious adverse reactions occurred in 57% of patients. The most common serious adverse reactions included encephalopathy (26%), infections (28%) and cytokine release syndrome (15%).

Grade 3 or higher adverse reactions were reported in 65% of patients. The most common Grade 3 or higher non-haematological adverse reactions included infections (32%) and encephalopathy (24%). The most common Grade 3 or higher haematological adverse reactions included neutropenia (99%), leukopenia (98%), lymphopenia (96%), thrombocytopenia (65%) and anaemia (56%).

Tabulated list of adverse reactions

Adverse reactions described in this section were identified in patients exposed to Tecartus in ZUMA-2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3 Adverse drug reactions identified with Tecartus

System Organ Class (SOC)	Frequency	Adverse reactions
Infections and infestations		
	Very common	Unspecified pathogen infections Viral infections Bacterial infections Fungal infections
Blood and lymphatic system disorders		
	Very common	Neutropenia[a] Lymphopenia[a] Leukopenia[a] Anaemia[a] Thrombocytopenia[a] Coagulopathy
Immune system disorders		
	Very common	Cytokine Release Syndrome[b] Hypogammaglobulinaemia
Metabolism and nutrition disorders		
	Very common	Hypophosphataemia[a] Decreased appetite
	Common	Dehydration Hypoalbuminemia[a]

System Organ Class (SOC)	Frequency	Adverse reactions
Psychiatric disorders		
	Very common	Insomnia Delirium Anxiety
Nervous system disorders		
	Very common	Encephalopathy Tremor Headache Aphasia Dizziness Neuropathy
	Common	Ataxia Seizure Increased intracranial pressure
Cardiac disorders		
	Very common	Tachycardias Bradycardias
	Common	Non-ventricular arrhythmias
Vascular disorders		
	Very common	Hypotension Hypertension Thrombosis
	Common	Haemorrhage
Respiratory, thoracic and mediastinal disorders		
	Very common	Cough Pleural effusion Dyspnoea Hypoxia
	Common	Respiratory failure Pulmonary oedema
Gastrointestinal disorders		
	Very common	Constipation Nausea Diarrhoea Oral pain Abdominal pain Vomiting Dysphagia
	Common	Dry mouth
Skin and subcutaneous tissue disorders		
	Very common	Rash
Musculoskeletal and connective tissue disorders		
	Very common	Motor dysfunction Musculoskeletal pain
Renal and urinary disorders		
	Very common	Renal insufficiency Urine output decreased
General disorders and administration site conditions		
	Very common	Fatigue Oedema Pyrexia Pain Chills
Investigations		
	Very common	Alanine aminotransferase increased[a] Aspartate aminotransferase increased[a] Hypokalaemia[a] Hyponatraemia[a] Hypocalcaemia[a] Blood uric acid increased[a]

System Organ Class (SOC)	Frequency	Adverse reactions
Only cytopenias that resulted in (i) new or worsening clinical sequelae or (ii) that required therapy or (iii) adjustment in current therapy are included in Table 3.		
[a] Frequency based on Grade 3 or higher laboratory parameter.		
[b] See section Description of selected adverse reactions.		

Description of selected adverse reactions

Cytokine release syndrome
CRS occurred in 91% of patients. Fifteen percent (15%) of patients experienced Grade 3 or higher (severe or life-threatening) CRS. The median time to onset was 3 days (range: 1 to 13 days) and the median duration was 10 days (range: 1 to 50 days). All patients (100%) recovered from CRS.

The most common signs or symptoms associated with CRS among the patients who experienced CRS included pyrexia (99%), hypotension (60%), hypoxia (37%), chills (33%), tachycardia (27%), headache (24%), fatigue (16%), nausea (13%), alanine aminotransferase increased (13%), aspartate aminotransferase increased (12%), diarrhoea (11%), and sinus tachycardia (11%). Serious adverse reactions that may be associated with CRS included hypotension, pyrexia, hypoxia, acute kidney injury, and tachycardia. See section 4.4 for monitoring and management guidance.

Neurologic events and adverse reactions
Neurologic adverse reactions occurred in 68% of patients. Thirty-three percent (33%) of patients experienced Grade 3 or higher (severe or life-threatening) adverse reactions. The median time to onset was 8 days (range: 1 to 262 days). Neurologic events resolved for 47 out of 56 patients with a median duration of 13 days (range: 1 to 567 days). Three patients had ongoing neurologic events at the time of death, including one patient with the reported event of serious encephalopathy and another patient with the reported event of serious confusional state. The remaining unresolved neurologic events were Grade 2. Eighty-five percent of all treated patients experienced the first CRS or neurological event within the first 7 days after Tecartus infusion.

The most common neurologic adverse reactions included encephalopathy (51%), tremor (38%), aphasia (20%), and delirium (18%). Serious adverse reactions including encephalopathy (26%), aphasia (6%) and seizure (2%) have been reported in patients administered with Tecartus. Serious cases of cerebral oedema which may become fatal have occurred in patients treated with Tecartus. See section 4.4 for monitoring and management guidance.

Febrile neutropenia and infections
Febrile neutropenia was observed in 6% of patients after Tecartus infusion. Infections occurred in 56% of patients in ZUMA-2. Grade 3 or higher (severe, life-threatening or fatal) infections occurred in 32% of patients including unspecified pathogen, bacterial, and viral infections in 26%, 6%, and 4% of patients respectively. See section 4.4 for monitoring and management guidance.

Prolonged cytopenias
Cytopenias are very common following prior lymphodepleting chemotherapy and Tecartus therapy.

Prolonged (present on or beyond Day 30 or with an onset at Day 30 or beyond) Grade 3 or higher cytopenias occurred in 55% of patients and included thrombocytopenia (38%), neutropenia (37%), and anaemia (17%). See section 4.4 for management guidance.

Hypogammaglobulinaemia
In ZUMA-2, hypogammaglobulinaemia occurred in 16% of patients. Grade 3 or higher hypogammaglobulinemia occurred in 1% of patients. See section 4.4 for management guidance.

Immunogenicity

The immunogenicity of Tecartus has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the

anti-CD19 CAR. To date, no anti-CD19 CAR T-cell antibody immunogenicity has been observed. Based on an initial screening assay, 17 patients tested positive for antibodies; however, a confirmatory orthogonal cell-based assay demonstrated that all 17 patients were antibody negative at all time points tested. There is no evidence that the kinetics of initial expansion, CAR T-cell function and persistence of Tecartus, or the safety or effectiveness of Tecartus, was altered in these patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There are no data regarding the signs of overdose with Tecartus.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: not yet assigned

Mechanism of action

Tecartus, a CD19-directed genetically modified autologous T-cell immunotherapy, binds to CD19 expressing cancer cells and normal B cells. Following anti-CD19 CAR T-cell engagement with CD19 expressing target cells, the CD28 co-stimulatory domain and CD3-zeta signalling domain activate downstream signalling cascades that lead to T-cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to killing of CD19-expressing cells.

Pharmacodynamic effects

In ZUMA-2, after Tecartus infusion, pharmacodynamic responses were evaluated over a 4-week interval by measuring transient elevation of cytokines, chemokines, and other molecules in blood. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF-α, interferon-gamma (IFN-γ) and IL-2 receptor alpha were analysed. Peak elevation was generally observed between 4 and 8 days after infusion and levels generally returned to baseline within 28 days.

Due to the on target, off-tumour effect of Tecartus a period of B-cell aplasia is expected following treatment.

Translational analyses performed to identify associations between cytokine levels and incidence of CRS or neurologic events showed that higher levels (peak and AUC at 1 month) of multiple serum analytes were associated with Grade 3 or higher neurologic adverse reactions and Grade 3 or higher CRS.

Clinical efficacy and safety

Relapsed or refractory MCL: ZUMA-2
The efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL who had previously received anthracycline or bendamustine-containing chemotherapy, an anti CD20 antibody, and a Bruton's tyrosine kinase inhibitor (BTKi) (ibrutinib or acalabrutinib), was evaluated in a phase 2 single-arm, open-label, multicenter trial. Eligible patients also had disease progression after last regimen or refractory disease to the most recent therapy. Patients with active or serious infections, prior allogeneic haematopoietic stem cell transplantation (HSCT), detectable cerebrospinal fluid

malignant cells or brain metastases, and any history of central nervous system lymphoma or CNS disorders were ineligible. In total, 74 patients were enrolled (*i.e.* leukapheresed) and 68 patients were treated with Tecartus. Three patients did not receive Tecartus due to manufacturing failure. Two other patients were not treated due to progressive disease (death) following leukapheresis. One patient was not treated with Tecartus after receiving lymphodepleting chemotherapy due to ongoing active atrial fibrillation. ITT was defined as all patients who underwent leukapheresis. A summary of the patient baseline characteristics is provided in Table 4.

Table 4 Summary of baseline characteristics for ZUMA-2

Category	**All leukapheresed (ITT) (N=74)**
Age (years)	
Median (min, max)	65 (38, 79)
≥ 65	58%
Male gender	84%
Median number of prior therapies (min, max)	3 (1; 5)
Relapsed/refractory subgroup	
Relapsed after auto-SCT	42%
Refractory to last MCL therapy	39%
Relapsed after last MCL therapy	19%
Patients with disease stage IV	86%
Patients with bone marrow involvement	51%
Morphological characteristic	
Classical MCL	54%
Blastoid MCL	26%
Other	1%
Unknown	19%
Received bridging therapy	
Yes	38%
No	62%
Ki-67 IHC by central laboratory	
N	49
Median	65%
Auto-SCT, autologous stem cell transplant; IHC, immunohistochemistry; Max, maximum; MCL, mantle cell lymphoma; Min, minimum;	

Tecartus was administered to patients as a single intravenous infusion at a target dose of 2×10^6 anti-CD19 CAR T cells/kg (maximum permitted dose: 2×10^8 cells) after lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously, both given on the 5th, 4th, and 3rd day before treatment. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was permitted to control disease burden.

For patients treated with Tecartus, the median time from leukapheresis to product release was 13 days (range: 9 to 20 days) and the median time from leukapheresis to Tecartus infusion was 27 days (range: 19 to 74 days, with the exception of one outlier of 134 days). The median dose was 2.0×10^6 anti-CD19 CAR T cells/kg. All patients received Tecartus infusion on day 0 and were hospitalized until day 7 at the minimum.

The primary endpoint was objective response rate (ORR) as determined by Lugano 2014 criteria by an independent review committee. Secondary endpoints included duration of response (DOR), overall survival (OS), progression free survival (PFS) and severity of adverse events.

An analysis set was defined a priori which consisted of the first 60 patients treated with Tecartus who were evaluated for response 6 months after the Week 4 disease assessment after Tecartus infusion. In this analysis set of 60 patients the ORR was 93% with a CR rate of 67%. The ORR was significantly higher than the prespecified historical control rate of 25% at a 1-sided significance level of 0.025 ($p < 0.0001$). Results in the ITT set are shown in Table 5.

Table 5 Summary of efficacy results for ZUMA-2

Category	**All leukapheresed [a](ITT) (N = 74)**
Objective response rate (ORR), n (%) [95% CI]	**62 (84%)** [73.4, 91.3]
CR n (%) [95% CI]	44 (59%) [47.4, 70.7]
PR n (%) [95% CI]	18 (24%) [15.1, 35.7]
Duration of response (DOR)[b]	
Median in months [95% CI]	NR [10.4, NE]
Range [c] in months	0.0+, 35.0+
Ongoing responses, CR+PR, CR, n (%) [d]	32 (43%), 30 (41%)
Progression free survival	
Median, months [95% CI]	16.2 [9.9, NE]
Overall survival	
Median, months [95% CI]	NR [24.6, NE]
6 month OS (%) [95% CI]	83.6 [72.9, 90.3]
12 month OS (%) [95% CI]	76.6 [65.1, 84.8]
24 month OS (%) [95% CI]	66.5 [52.8, 77.1]
Median Follow-up in months (min, max)	16.8 [7.2, 37.6]

CI, confidence interval; CR, complete remission; ITT, intent to treat; NE, not estimable; NR, not reached; OS, overall survival; PR, partial remission.

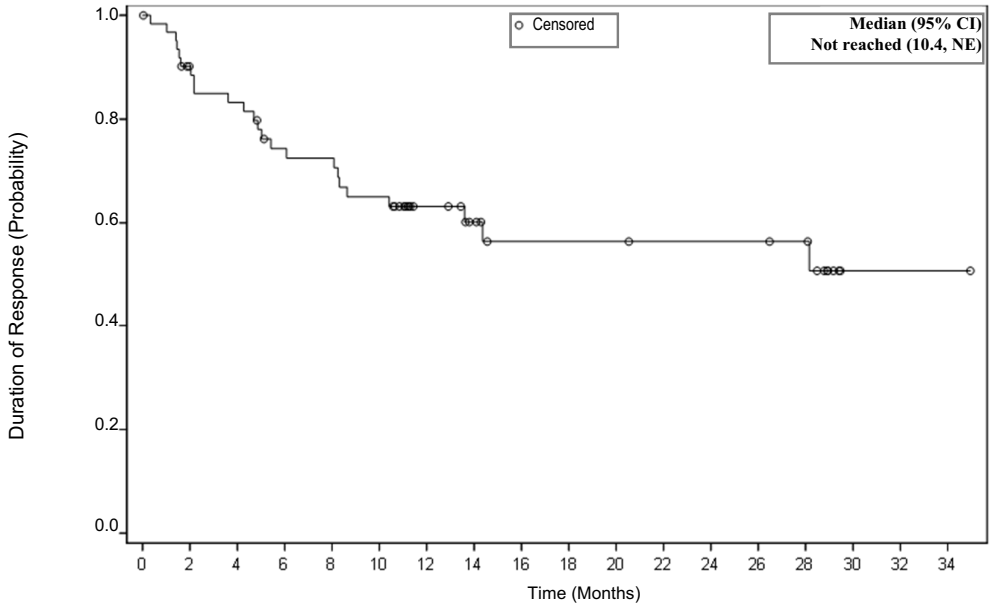
a Of the 74 patients that were enrolled (*i.e.* leukapheresed), 69 patients received lymphodepleting chemotherapy, and 68 patients received Tecartus.

b Among all responders. DOR is measured from the date of first objective response to the date of progression or death.

c A + sign indicates a censored value.

d At the data cutoff date. Percentages are calculated using the total number of patients in the analysis set as the denominator.

Figure 1 Kaplan Meier DOR in the intent to treat set



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Tecartus in all subsets of the paediatric population in treatment of mantle cell lymphoma (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme.
This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Following infusion of Tecartus, anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Peak levels of anti-CD19 CAR T cells occurred within the first 7 to 15 days after the infusion.

The number of anti-CD19 CAR T cells in blood was associated with objective response (CR or PR) (Table 6).

Table 6 Kinetic parameters of autologous anti-CD19-transduced CD3+ cells in ZUMA-2

Number of anti-CD19 CAR T cell	**Responding patients (CR or PR) (N=63)**	**Non-responding patients (N=5)**	**P-Value**
Peak (cells/µL) Median [min; max], n	97.52 [0.24, 2589.47], 62	0.39 [0.16, 22.02], 5	0.0020
AUC_{0-28} (cells/µL·days) Median [min; max], n	1386.28 [3.83 to 2.77×10^4], 62	5.51 [1.81, 293.86], 5	0.0013

P-value is calculated by Wilcoxon test

Median peak anti-CD19 CAR T-cell values were 74.08 cells/μL in patients ≥65 years of age (n=39) and 112.45 cells/μL in patients <65 years of age (n=28). Median anti-CD19 CAR T-cell AUC values were 876.48 cells/μL·day in patients ≥65 years of age and 1640.21 cells/μL·day in patients <65 years of age.

Gender had no significant impact on $AUC_{Day\ 0–28}$ and C_{max} of Tecartus.

Studies of Tecartus in patients with hepatic and renal impairment were not conducted.

5.3 Preclinical safety data

Tecartus comprises engineered human T cells; therefore, there are no representative *in vitro* assays, *ex vivo* models, or *in vivo* models that can accurately address the toxicological characteristics of the human product. Hence, traditional toxicology studies used for medicinal product development were not performed.

No carcinogenicity or genotoxicity studies have been conducted.

No studies have been conducted to evaluate the effects of this treatment on fertility, reproduction, and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cryostor CS10
Sodium chloride
Human albumin

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Tecartus is stable for 1 year when stored frozen in the vapour phase of liquid nitrogen (≤ − 150°C).

Tecartus is stable at room temperature (20 °C to 25 °C) for up to 3 hours after thawing. However, Tecartus infusion should begin within 30 minutes of thaw completion and the total infusion time should not exceed 30 min. Thawed product should not be refrozen.

6.4 Special precautions for storage

Tecartus must be stored in the vapour phase of liquid nitrogen (≤ − 150 °C) and must remain frozen until the patient is ready for treatment to ensure viable live autologous cells are available for patient administration.

For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Ethylene-vinyl acetate cryostorage bag with sealed addition tube and two available spike ports, containing approximately 68 mL of cell dispersion.

One cryostorage bag is individually packed in a shipping metal cassette.

6.6 Special precautions for disposal and other handling

Irradiation could lead to inactivation of the product.

Precautions to be taken for the transport and disposal of the medicinal product

Tecartus should be transported within the facility in closed, break-proof, leak-proof containers.

Tecartus contains genetically modified human blood cells. Local guidelines on handling of waste of human-derived material should be followed for unused medicinal products or waste material. All material that has been in contact with Tecartus (solid and liquid waste) should be handled and disposed of in accordance with local guidelines on handling of waste of human-derived material.

Accidental exposure to Tecartus must be avoided. Local guidelines on handling of human-derived material should be followed in case of accidental exposure, which may include washing of the contaminated skin and removal of contaminated clothes. Work surfaces and materials which have potentially been in contact with Tecartus must be decontaminated with appropriate disinfectant.

7. MARKETING AUTHORISATION HOLDER

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1492/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 December 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance

Kite Pharma, Inc.
2355 Utah Avenue
El Segundo
California
CA 90245
United States

Name and address of the manufacturer(s) responsible for batch release

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Key elements:

Availability of tocilizumab and site qualification

To minimise the risks associated with the treatment of Tecartus, the MAH must ensure that hospitals and their associated centres that dispense Tecartus are specially qualified in accordance with the agreed controlled distribution program.

The MAH must ensure on-site, immediate access to at least 1 dose of tocilizumab for each patient as cytokine release syndrome (CRS) management medication prior to treating patients. Hospitals and their associated centres should have access to an additional dose of tocilizumab within 8 hours of each previous dose.

Tecartus will only be supplied to hospitals and associated centres that are qualified and only if the healthcare professionals (HCP) involved in the treatment of a patient have completed the educational program.

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

HCP Educational program

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:

- provide information about the safety and efficacy long-term follow up study and the importance of contributing to such a study
- 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
- ensure that detailed instructions about the thawing procedure are provided
- before treating a patient, ensure that at least 1 dose of tocilizumab for each patient is available on site. The qualified treatment centre must have access to additional doses of tocilizumab within 8 hours

Patient Educational program

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

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to further characterise the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory Mantle cell Lymphoma (MCL) the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.	Interim reports to be submitted in accordance with the RMP. 30 June 2042

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL and the Benefit/Risk balance in the female, elderly and severely diseased patients, the MAH shall submit the results of a prospective study investigating efficacy and safety based on data from the same registry used to characterise the long-term efficacy and safety of Tecartus, according to an agreed protocol.	30 September 2025
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL the MAH shall submit the 24 months follow-up data from all treated patients in cohort 1 of the pivotal study ZUMA-2.	31 March 2022

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

METAL CASSETTE

1. NAME OF THE MEDICINAL PRODUCT

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion
autologous anti-CD19-transduced CD3+ cells (CAR+ viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous human T cells transduced with retroviral vector encoding an anti-CD19 chimeric antigen receptor (CAR) with a target dose of 2 × 10^6 anti-CD19 CAR positive viable T cells/kg.

3. LIST OF EXCIPIENTS

Excipients: Cryostor CS10, human albumin, sodium chloride.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
One sterile infusion bag.
Contents: approximately 68 mL of cell dispersion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Do not irradiate.
For intravenous use only.
Gently mix the contents of the bag while thawing.
Do NOT use a leukodepleting filter.
STOP confirm patient ID prior to infusion.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store frozen in vapour phase of liquid nitrogen ≤ − 150 °C.
Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Contains genetically-modified cells.
Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1492/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot:
Kite Patient ID:
Additional Patient ID:
Patient Name:
Patient DOB:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INFUSION BAG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion
autologous anti-CD19-transduced CD3+ cells (CAR+ viable T cells)
For intravenous use only.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot:
Kite Patient ID:
Additional Patient ID:
Patient Name:
Patient DOB:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Contents: approximately 68 mL of cell dispersion.

6. OTHER

For autologous use only.
Verify patient ID.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion
autologous anti-CD19-transduced CD3+ cells (CAR+ viable T cells)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will give you a Patient Alert Card. Read it carefully and follow the instructions on it.
- Always show the Patient Alert Card to the doctor or nurse when you see them or if you go to hospital.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tecartus is and what it is used for

Tecartus is a gene therapy medicine used for treating mantle cell lymphoma in adults. It is used when other medicines have stopped working for you (relapsed or refractory mantle cell lymphoma). The medicine is made specially for you from your own white blood cells that have been modified and are known as autologous anti-CD19-transduced CD3+ cells.

Mantle cell lymphoma is a cancer of a part of the immune system (the body's defences). It affects a type of white blood cell called B-lymphocytes. In mantle cell lymphoma, B-lymphocytes grow in an uncontrolled way and build up in the lymph tissue, bone marrow or blood.

How Tecartus works
The white blood cells are taken from your blood and are genetically modified so that they can target the cancer cells in your body. When Tecartus is infused into your blood, the modified white blood cells will kill the cancer cells.

2. What you need to know before you are given Tecartus

You are not to be given Tecartus
- if you are allergic to any of the ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.
- if you can't receive the medicine to reduce the number of white blood cells in your blood (*lymphodepleting chemotherapy*) (see also section 3, How Tecartus is given).

Warnings and precautions
Tecartus is made from your own white blood cells and should only be given to you (*autologous use*).

Tests and checks
Before you are given Tecartus your doctor will:
- Check your lungs, heart, kidney and blood pressure.
- Look for signs of infection or inflammation; and decide whether you need to be treated before you are given Tecartus.
- Check if your cancer is getting worse.
- Look for signs of graft-versus-host disease that can happen after a transplant. This happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhoea and bloody stools.
- Check your blood for uric acid and for how many cancer cells there are in your blood. This will show if you are likely to develop a condition called *tumour lysis syndrome.* You may be given medicines to help prevent the condition.
- Check for hepatitis B, hepatitis C or HIV infection.
- Check if you had a vaccination in the previous 6 weeks or are planning to have one in the next few months.
- Check if you have previously received a treatment that attaches to the protein called CD19.

In some cases, it might not be possible to go ahead with the planned treatment with Tecartus. If Tecartus infusion is delayed for more than 2 weeks after you have received lymphodepleting chemotherapy you may have to receive more chemotherapy (see also section 3, How Tecartus is given).

After you have been given Tecartus
Tell your doctor or nurse immediately or get emergency help right away if you have any of the following:
- Chills, extreme tiredness, weakness, dizziness, headache, cough, shortness of breath, rapid or irregular heartbeat, severe nausea, vomiting, or diarrhoea which may be symptoms of a condition known as *cytokine release syndrome.* Take your temperature twice a day for 3 to 4 weeks after treatment with Tecartus. If your temperature is high, see your doctor immediately.
- Fits, shaking, or difficulty speaking or slurred speech, loss of consciousness or decreased level of consciousness, confusion and disorientation, loss of balance or coordination.
- Fever (e.g. temperature above 38°C), which may be a symptom of an infection.
- Extreme tiredness, weakness and shortness of breath, which may be symptoms of a lack of red blood cells.
- Bleeding or bruising more easily, which may be symptoms of low levels of cells in the blood known as platelets.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse.

Your doctor will regularly check your blood counts as the number of blood cells and other blood components may decrease.

You will be asked to enrol in a registry for at least 15 years in order to better understand the long-term effects of Tecartus.

Do not donate blood, organs, tissues, or cells for transplants.

Children and adolescents
Tecartus should not be used in children and adolescents below 18 years of age.

Other medicines and Tecartus
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

Before you are given Tecartus tell your doctor or nurse if you are taking any medicines that weaken your immune system such as corticosteroids, since these medicines may interfere with the effect of Tecartus.

In particular, you must not be given certain vaccines called live vaccines:
- In the 6 weeks before you are given the short course of lymphodepleting chemotherapy to prepare your body for the Tecartus cells.
- During Tecartus treatment.
- After treatment while the immune system is recovering.

Talk to your doctor if you need to have any vaccinations.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine. This is because the effects of Tecartus in pregnant or breast-feeding women are not known, and it may harm your unborn baby or your breast-fed child.
- If you are pregnant or think you may be pregnant after treatment with Tecartus, talk to your doctor immediately.
- You will be given a pregnancy test before treatment starts. Tecartus should only be given if the results show you are not pregnant.

Discuss pregnancy with your doctor if you have received Tecartus.

Driving and using machines
Tecartus can cause problems such as altered or decreased consciousness, confusion and seizures (fits) in the 8 weeks after it is given.

Do not drive, use machines, or take part in activities that need you to be alert for at least 8 weeks after your Tecartus treatment or until your doctor tells you that you have completely recovered.

Tecartus contains sodium, dimethylsulfoxide (DMSO) and gentamicin
This medicine contains 300 mg sodium (main component of cooking/table salt) in each infusion. This is equivalent to 15% of the recommended maximum daily dietary intake of sodium for an adult. It also contains DMSO and gentamicin which may cause severe hypersensitivity reactions.

3. How Tecartus is given

Tecartus will always be given to you by a healthcare professional.

- Since Tecartus is made from your own white blood cells, your cells will be collected from you to prepare your medicine. Your doctor will take some of your blood using a catheter placed in your vein (a procedure call *leukapheresis*). Some of your white blood cells are separated from your blood and the rest of your blood is returned to your vein. This can take 3 to 6 hours and may need to be repeated.
- Your white blood cells are sent away to a manufacturing center to make your Tecartus. It usually takes about 2 to 3 weeks to make Tecartus but the time may vary.

Medicines given before Tecartus treatment
A few days before you receive Tecartus, you will be given lymphodepleting chemotherapy, which will allow the modified white blood cells in Tecartus to multiply in your body when the medicine is given to you.

During the 30 to 60 minutes before you are given Tecartus you may be given other medicines. This is to help prevent infusion reactions and fever. These other medicines may include:
- Paracetamol.
- An antihistamine such as diphenhydramine.

How you are given Tecartus
Tecartus will always be given to you by a doctor in a qualified treatment centre.

- Tecartus is given in a single dose.
- Your doctor or nurse will give you a single infusion of Tecartus through a catheter placed into your vein (*intravenous infusion*) over about 30 minutes.
- Tecartus is the genetically modified version of your white blood cells. Your healthcare professional handling the treatment will therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases and will follow local guidelines on handling of waste of human-derived material to clean up or dispose of any material that has been in contact with it.

After you are given Tecartus
- You should stay close to the hospital where you were treated for at least 4 weeks after Tecartus treatment. Your doctor will recommend that you return to the hospital daily for at least 10 days or that you stay at the hospital as an in-patient for the first 10 days after Tecartus treatment. This is so your doctor can check if your treatment is working and help you if you have any side effects.

If you miss any appointments, call your doctor or your treatment centre as soon as possible to reschedule your appointment.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Do not try to treat your side effects on your own.

Tecartus can cause side effects that may be serious or life-threatening. **Get urgent medical attention** if you get any of the following side effects after the Tecartus infusion.

Very common: may affect more than 1 in 10 people
- Fever, chills, reduced blood pressure which may cause symptoms such as dizziness, lightheadedness, fluid in the lungs, which may be severe and can be fatal (all symptoms of a condition called *cytokine release syndrome*).
- Loss of consciousness or decreased level of consciousness, confusion or memory loss due to disturbances of brain function, difficulty speaking or slurred speech, involuntary shaking (*tremor*), fits (*seizures*), sudden confusion with agitation, disorientation, hallucination or irritability (*delirium*).
- Fever, chills, which may be signs of an infection.

Other possible side effects
Other side effects are listed below. If these side effects become severe or serious, tell your doctor immediately.

Very common: may affect more than 1 in 10 people
- Abnormally low number of white blood cells, which may increase your risk of infection.
- Low number of cells that help clot the blood *(thrombocytopenia)*, alteration of the blood's ability to form clots: symptoms can include excessive or prolonged bleeding or bruising.
- High blood pressure.
- Decrease in the number of red blood cells (cells that carry oxygen): symptoms can include extreme tiredness with a loss of energy.

– Extreme tiredness.
– Fast or slow heartbeat.
– Decrease of oxygen reaching body tissues: symptoms can include changes to the colour of your skin, confusion, rapid breathing.
– Shortness of breath, cough.
– Nausea, constipation, diarrhoea, abdominal pain, vomiting, difficulty swallowing.
– Muscle pain, joint pain, bone pain, pain in the extremities of the body.
– Lack of energy or strength, muscular weakness, difficulty moving, muscle spasm.
– Headache.
– Kidney problems causing your body to hold onto fluid, build-up of fluids in tissue *(oedema)* which can lead to weight gain and difficulty in breathing, decrease output of urine.
– High levels of uric acid seen in blood tests.
– Low levels of sodium, phosphate, potassium or calcium seen in blood tests.
– Decreased appetite, sore mouth.
– Difficulty sleeping, anxiety.
– Swelling in the limbs, fluid around the lungs *(pleural effusion)*.
– Skin rash.
– Low levels of immunoglobulins seen in blood test, which may lead to infections.
– Increase in liver enzymes seen in blood tests.
– Blood clots: symptoms can include pain in the chest or upper back, difficulty breathing, coughing up blood or cramping pain, swelling in a single leg, warm and darkened skin around the painful area.
– Nerve pain.

Common: may affect up to 1 in 10 people
– Low levels of albumin seen in blood tests.
– Excessive bleeding.
– Irregular heartbeat *(arrhythmia)*.
– Loss of control of body movements.
– Dry mouth, dehydration.
– Breathlessness *(respiratory failure)*.
– Difficulty breathing which makes you unable to speak in full sentence, cough due to fluid in the lungs.
– Increase of the pressure inside your skull.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Tecartus

The following information is intended for doctors only.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the container label and infusion bag after EXP.

Store frozen in vapour phase of liquid nitrogen ≤ − 150 °C until thawed for use.
Do not refreeze.

This medicine contains genetically modified human blood cells. Local guidelines on handling of waste of human-derived material should be followed for unused medicinal product or waste material. As this

medicine will be given by qualified healthcare professionals, they are responsible for the correct disposal of the product. These measures will help protect the environment.

6. Contents of the pack and other information

What Tecartus contains
The active substance is autologous anti-CD19-transduced CD3+ cells. Each patient-specific single infusion bag contains a dispersion of anti-CD19 CAR T cells in approximately 68 mL for a target dose of 2×10^6 anti-CD19 CAR-positive viable T cells/kg.
The other ingredients (excipients) are: Cryostor CS10, sodium chloride, human albumin. See section 2 "Tecartus contains sodium".

What Tecartus looks like and contents of the pack
Tecartus is a clear to opaque, white to red dispersion for infusion, supplied in an infusion bag individually packed in a metal cassette. A single infusion bag contains approximately 68 mL of cell dispersion.

Marketing Authorisation Holder
Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

Manufacturer
Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
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Tél/Tel: + 32 (0) 24 01 35 50

България
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Suomi/Finland
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Puh/Tel: + 46 (0) 8 5057 1849

Sverige
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United Kingdom
Gilead Sciences Ltd
Tel: + 44 (0) 8000 113700

This leaflet was last revised in

This medicine has been given ‘conditional approval’.
This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

<--->

The following information is intended for healthcare professionals only:

It is important that you read the entire content of this procedure prior to administering Tecartus.

Precautions to be taken before handling or administering the medicinal product

- Tecartus contains genetically-modified cells. Local guidelines on handling of human-derived material applicable for such products should be followed.
- Tecartus should be transported within the facility in closed, break-proof, leak-proof containers.
- Tecartus is prepared from autologous blood of the patient collected by leukapheresis. Patient leukapheresis material and Tecartus may carry a risk of transmitting infectious viruses to healthcare professionals (HCP) handling the product. Accordingly, HCP should employ appropriate precautions (wearing gloves and glasses) when handling leukapheresis material or Tecartus to avoid potential transmission of infectious diseases.

Preparation for infusion

- Verify that the patient's identity (ID) matches the patient identifiers on the Tecartus metal cassette.
- The Tecartus infusion bag must not be removed from the metal cassette if the information on the patient-specific label does not match the intended patient.
- Once the patient's ID is confirmed, remove the infusion bag from the metal cassette.
- Check that the patient information on the metal cassette label matches that on the bag label.
- Inspect the infusion bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines for handling of waste of human-derived material (or immediately contact Kite).
- Place the infusion bag inside a second bag.
- Thaw Tecartus at approximately 37 °C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Tecartus should not be washed, spun down, and/or re-suspended in new media prior to infusion. Thawing should take approximately 3 to 5 minutes.
- Once thawed, Tecartus is stable at room temperature (20 °C – 25 °C) for up to 3 hours. However, the infusion should begin within 30 minutes of thaw completion.

Do NOT use a leukodepleting filter.

Administration

- The medicine must be administered in a qualified treatment centre by a physician(s) with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Tecartus.
- Ensure that at least 1 dose of tocilizumab per patient and emergency equipment are available prior to infusion and during the recovery period. Hospitals and associated centres should have access to an additional dose of tocilizumab within 8 hours of each previous dose.
- The patient's identity should be matched with the patient identifiers on the infusion bag.
- Tecartus is for autologous use only.
- Tecartus should be administered as an intravenous infusion using latex-free intravenous tubing without a leukocyte depleting filter within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the bag during infusion to prevent cell clumping. All contents of the infusion bag should be infused.
- Sterile sodium chloride 9 mg/mL (0.9%) (0.154 mmol sodium per mL) solution for injection should be used to prime the tubing prior to infusion as well as rinse it afterwards. When the full volume of Tecartus has been infused, the infusion bag should be rinsed with 10 to 30 mL sodium chloride 9 mg/mL (0.9%) solution for injection by back priming to ensure as many cells as possible are infused into the patient.

Disposal of Tecartus

- Any unused medicinal product or waste material that has been in contact with Tecartus (solid and liquid waste) should be handled and disposed of in accordance with local guidelines on handling of waste of human-derived material. Work surfaces and material which have potentially been in contact with Tecartus must be decontaminated with appropriate disinfectant.

Accidental exposure

- Accidental exposure to Tecartus must be avoided. Local guidelines on handling of human-derived material should be followed in case of accidental exposure, which may include washing of the contaminated skin, removal of contaminated clothes.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.

Appendix 5. EBMT Cellular and Gene Therapy Form

CELLULAR THERAPIES FORM
-- Pre-Infusion Registration --

INFORMED CONSENT

Was the patient asked to consent to data submission?	☐ **No**	☐ **Yes**	
Date of informed consent: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*			
Is your centre using the EBMT consent form?	☐ **No**	☐ **Yes**	
Did the patient consent to data sharing with health authorities and/or researchers?	☐ **No**	☐ **Yes**	☐ **Unknown**
Did the patient consent to data sharing with Health Technology Assessment bodies (HTA)?	☐ **No**	☐ **Yes**	☐ **Unknown**
Did the patient consent to data sharing with Market Authorisation Holders (MAH)?	☐ **No**	☐ **Yes**	☐ **Unknown**
Did the patient consent to their medical records being reviewed?	☐ **No**	☐ **Yes**	☐ **Unknown**

CENTRE IDENTIFICATION

EBMT Centre Identification Code (CIC): _____

Hospital: _____

Unit: _____

Type of unit or team responsible for this cellular therapy:
(Optional; this is a coded replication of the above unit field and can be used by centres that have more than one department/unit reporting to the EBMT)

- ☐ Adults
- ☐ Allograft
- ☐ Autograft
- ☐ BMT unit
- ☐ Dept. Medicine
- ☐ Haematology
- ☐ Oncology
- ☐ Paediatrics
- ☐ Paediatric haematology
- ☐ Paediatric oncology

Contact person: _____

PATIENT DATA

EBMT Unique Identification Code (UIC): _____
(Patient number in EBMT database; complete if patient had a previous treatment and is already registered in the database)

Date of this report: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Hospital Unique Patient Number or code (UPN): _____
(Compulsory; registrations will not be accepted without this item. All treatments (transplants and CAR T-cell) performed in the same patient must be registered with the same patient identification number or code as this belongs to the patient and not to the treatment.)

Other type of patient identification code(s): _____
(Optional; to be used by the centre to register a patient code for internal use as necessary)

Date of birth: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Sex *(at birth)*:
☐ Male
☐ Female

Initials: _____ / _____ *(first name(s) / family name(s))*

ABO group:
☐ A
☐ B
☐ AB
☐ O

Rh factor:
☐ Absent
☐ Present
☐ Not evaluated

If the patient had a previous cellular therapy or a stem cell transplant, please make sure that this previous treatment is registered and that the latest follow-up has been recorded using the appropriate follow-up form before proceeding; this is so relapse data and other events between transplants/advanced cellular therapies can be captured.

INDICATION FOR CELLULAR THERAPY

☐ **Treatment of a primary disease:**

Indicate below for which disease this cellular therapy has been received.

☐ Primary Acute Leukaemia	
Acute Myelogenous Leukaemia (AML)	*(page 8)*
Precursor Lymphoid Neoplasms (previously ALL)	*(page 12)*
Other Primary Acute Leukaemia	*(page 15)*
☐ Chronic Leukaemia	
Chronic Myeloid Leukaemia (CML)	*(page 16)*
Chronic Lymphocytic Leukaemia (CLL)	*(page 16)*
Prolymphocytic Leukaemias (PLL) and Other Chronic Leukaemias	*(page 17)*
☐ Lymphoma	
Non-Hodgkin Lymphoma (NHL)	*(page 19)*
Hodgkin's Lymphoma (HL)	*(page 23)*
Immunodeficiency-associated lymphoproliferative disorders (including PTLD)	*(page 23)*
☐ Myelodysplastic Syndromes (MDS) and/or Myeloproliferative Neoplasm (MPN)	
MDS	*(page 24)*
MDS/MPN	*(page 26)*
MPN	*(page 28)*
☐ Plasma Cell Disorders (PCD including Multiple Myeloma (MM)	*(page 31)*
☐ Bone Marrow Failure Syndromes including Aplastic Anaemia	*(page 33)*
☐ Haemoglobinopathy	*(page 34)*
☐ Solid Tumour	*(page 35)*
☐ Inherited Disorders	
Primary immune deficiencies (PID)	*(page 37)*
Metabolic disorders	*(page 38)*
Platelet and other inherited disorder	*(page 39)*
☐ Histiocytic disorders	*(page 40)*
☐ Autoimmune disease	
Connective tissue	*(page 41)*
Vasculitis	*(page 41)*
Arthritis	*(page 41)*
Neurological	*(page 42)*
Haematological	*(page 42)*
Bowel disorder	*(page 42)*
Other autoimmune disease (Diabetes, etc.)	*(page 42)*
☐ Infections	*(page 43)*
☐ Other primary disease; specify: _____	*(page 44)*

Complete and attach the relevant disease classification sheet as per page numbers indicated above.

Date of diagnosis: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

INDICATION FOR CELLULAR THERAPY continued

☐ **Treatment or prevention of complications**
(derived from a previous treatment including HSCT or expected from a subsequent treatment)

Before continuing please make sure that the above mentioned transplant/ cellular therapy has been registered and that a MED-A annual follow-up form has been submitted; this is so relapse data and other events between transplants and/or cellular therapies can be captured.

☐ **Both, treatment of primary disease and complication**
Complete and attach the relevant disease classification sheet as per page numbers indicated above.

BASIC INFORMATION ON THE PLANNED CELLULAR THERAPY

Clinical setting:
(select only one)

☐ As per marketing approval / Standard of care / Institutional guidelines

☐ Hospital exemption

☐ Compassionate use / Accelerated access

☐ Investigational drug product (IDP)/ Clinical trial (CT)

Phase: ☐ 1 ☐ 1/2 ☐ 2 ☐ 2/3 ☐ 3
Blind trial: ☐ No ☐ Yes
Randomised trial: ☐ No ☐ Yes

Eudract number: _____
USA NCT number: _____
UMIN CT number: _____

☐ Unknown

Cell origin:

☐ Autologous --> *Continue with 'Planned Cellular Therapy Product' on page 5*

☐ Allogeneic

This product is manufactured from:

☐ A known donor never used to treat this patient *(e.g. from a donor registry or related)*
--> *Complete 'Donor' section on page 5*

☐ A donor that is already registered as part of a previous treatment
--> *Skip 'Donor' section and continue with 'Planned Cellular Therapy Product' on page 5*

☐ An unknown donor with no data available *(e.g. from a commercial product)*
--> *Skip 'Donor' section and continue with 'Planned Cellular Therapy Product' on page 5*

DONOR INFORMATION

Date of birth: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* *OR* **Age at time of donation :** _____ *(years)* _____ *(months)*
(only if date of birth not provided)

Sex ***(at birth)*****:**
☐ Male
☐ Female

Donor Identification:

Donor ID given by the treating centre *(mandatory)*: _____

Global registration identifier for donors: _____

Donor ID given by the Donor Registry or Cord Blood Bank: _____

ION code of the Donor Registry or Cord Blood Bank *(mandatory)*: _____

EuroCord code for the Cord Blood Bank *(if applicable)*: _____

Name of Donor Registry or Cord Blood Bank: _____

PLANNED CELLULAR THERAPY PRODUCT
Description

If more than one planned cellular therapy product please replicate this section for each one of them.

Is the planned cellular therapy product a commercial product?
☐ No
☐ Yes

Will the planned cellular therapy product consist of more than one cell infusion unit?
☐ No
☐ Yes: Number of different cell infusion units: _____

PLANNED CELLULAR THERAPY INFUSION PRODUCT
Description continued

If more than one planned cellular therapy product please replicate this section for each one of them.

Identification:

Name of manufacturer:

- ☐ Autolus
- ☐ Bluebird Bio
- ☐ Celgene/ Bristol Myer Squibb
- ☐ Celyad
- ☐ GlaxoSmithKline (GSK)
- ☐ Janssen (Johnson & Johnson)
- ☐ Kite Gilead
- ☐ Miltenyi
- ☐ Novartis
- ☐ Orchard
- ☐ Vertex
- ☐ Local hospital or university
- ☐ Other; specify: _____

Name of product *(if applicable)*:

- ☐ Abecma
- ☐ Breyanzi
- ☐ Cilta-cel
- ☐ Eli-cel
- ☐ Kymriah
- ☐ Tecartus
- ☐ Yescarta
- ☐ Other; specify: _____

Tissue source:

- ☐ Bone Marrow
- ☐ Peripheral Blood
- ☐ Umbilical Cord Blood
- ☐ Tumour
- ☐ Other; specify: _____

Collection procedure:

Date of collection: _ _ _ _ / _ _ /_ _ *(YYYY/MM/DD)*
(If more than one collection enter the date of the first collection.)

Number of collections: _____

END OF GENERAL PRE-INFUSION REGISTRATION

To complete PRE-INFUSION REGISTRATION please fill in the applicable disease classification.

ACUTE LEUKAEMIAS
Acute Myeloid Leukaemias (AML) - *main disease code 1*

DISEASE

Classification:

AML with recurrent genetic abnormalities

- ☐ AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
- ☐ AML with inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); CBFB-MYH11
- ☐ Acute promyelocytic leukaemia with t(15;17)(q22;q12); PML/RARA
- ☐ AML with t(9;11) (p22;q23); MLLT3-MLL
- ☐ AML with t(6;9) (p23;q24); DEK-NUP214
- ☐ AML with inv(3) (q21;q26.2) or t(3;3) (q21;q26.2); RPN1-EVI1
- ☐ AML (megakaryoblastic) with t(1;22) (p13;q13); RBM15-MKL1
- ☐ AML with myelodysplasia related changes (previously “Acute Leukaemia transformed from MDS or MDS/MPN”):
  Was there a previous diagnosis of MDS or MDS/MPN?
  - ☐ No *(continue with 'Predisposing Condition'* below)
  - ☐ Yes *(fill in the MDS (page 24) or MDS/MPN (page 26); then continue with 'Predisposing Condition' below)*
- ☐ AML with 11q23 (MLL) abnormalities
- ☐ AML with BCR-ABL1
- ☐ AML with mutated NPM1
- ☐ AML with biallelic mutation of CEBPA
- ☐ AML with mutated RUNX1

AML not otherwise categorised (NOS)

- ☐ AML with minimal differentiation (FAB M0)
- ☐ AML without maturation (FAB M1)
- ☐ AML with maturation (FAB M2)
- ☐ Acute myelomonocytic leukaemia (FAB M4)
- ☐ Acute monoblastic and monocytic leukaemia (FAB M5)
- ☐ Acute erythroid leukaemia (FAB M6)
- ☐ AML (megakaryoblastic) with t(1;22) (p13;q13); RBM15-MKL1
- ☐ Acute megakaryoblastic leukaemia (FAB M7)
- ☐ Acute basophilic leukaemia
- ☐ Acute panmyelosis with myelofibrosis

- ☐ Myeloid sarcoma
- ☐ Myeloid proliferations related to Down Syndrome
- ☐ Blastic plasmacytoid dendritic cell neoplasm (BPDCN)
- ☐ Therapy related myeloid neoplasia (previously “Secondary Acute Leukaemia”; related to prior treatment but NOT after a previous diagnosis of MDS or MDS/MPN .)

ACUTE LEUKAEMIAS
Acute Myeloid Leukaemias (AML) - *main disease code 1*

DISEASE continued

Did the patient have a predisposing condition prior to the diagnosis of leukaemia?

☐ No

☐ Yes:
- ☐ Aplastic Anaemia
- ☐ Bloom Syndrome
- ☐ Fanconi Anaemia
- ☐ Unknown

Is this a donor cell leukaemia?
(Only applicable if the patient has received an allograft prior to the diagnosis of acute leukaemia.)

☐ No

☐ Yes

☐ Not evaluated

CHROMOSOME ANALYSIS

Chromosome analysis at diagnosis *(all methods including FISH)*:
(Include all analyses before treatment; describe results of the most recent complete analysis)

☐ Normal		
☐ Abnormal:	Complex karyotype: *(3 or more abnormalities)*	☐ No ☐ Yes ☐ Unknown
	Monosomal karyotype: *(≥2 autosomal monosomies or 1 autosomal monosomie + at least 1 structural abnormality)*	☐ No ☐ Yes ☐ Unknown
☐ Not done or failed		
☐ Unknown		

ACUTE LEUKAEMIAS
Acute Myeloid Leukaemias (AML) - *main disease code 1*

CHROMOSOME ANALYSIS continued

Transcribe the complete karyotype: ____

OR

Indicate below whether the abnormalities were absent, present or not evaluated.

t(15;17)	☐ Absent ☐ Present ☐ Not evaluated
t(8;21)	☐ Absent ☐ Present ☐ Not evaluated
inv(16)/ t(16;16)	☐ Absent ☐ Present ☐ Not evaluated
11q23 abnormality type *(fill in only if a 11q23 abnormality is present)*:	☐ Absent ☐ Present ☐ Not evaluated
t(9;11)	☐ Absent ☐ Present ☐ Not evaluated
t(11;19)	☐ Absent ☐ Present ☐ Not evaluated
t(10;11)	☐ Absent ☐ Present ☐ Not evaluated
t(6;11)	☐ Absent ☐ Present ☐ Not evaluated
Other abn(11q23); specify: ___________	☐ Absent ☐ Present
3q26 (EVI1) abnormality type *(fill in only if a 3q26 abnormality is present)*:	☐ Absent ☐ Present ☐ Not evaluated
inv(3) / t(3;3)	☐ Absent ☐ Present ☐ Not evaluated
t(2;3)(p21;q26)	☐ Absent ☐ Present ☐ Not evaluated
Other (3q26)/EVI1 rearrangement; specify: ___________	☐ Absent ☐ Present
t(6;9)	☐ Absent ☐ Present ☐ Not evaluated
abn 5 type *(fill in only if an abn 5 is present)*:	☐ Absent ☐ Present ☐ Not evaluated
del (5q)	☐ Absent ☐ Present ☐ Not evaluated
monosomy 5	☐ Absent ☐ Present ☐ Not evaluated
Add(5q)	☐ Absent ☐ Present ☐ Not evaluated
Other abn(5q); specify: ___________	☐ Absent ☐ Present
abn 7 type *(fill in only if an abn 7 is present)*:	☐ Absent ☐ Present ☐ Not evaluated
del(7q)	☐ Absent ☐ Present ☐ Not evaluated
monosomy 7	☐ Absent ☐ Present ☐ Not evaluated
add(7q)	☐ Absent ☐ Present ☐ Not evaluated
Other abn(7q); specify: ___________	☐ Absent ☐ Present
-17	☐ Absent ☐ Present ☐ Not evaluated
abn(17p)	☐ Absent ☐ Present ☐ Not evaluated
t(1;22)	☐ Absent ☐ Present ☐ Not evaluated
Trisomy 8	☐ Absent ☐ Present ☐ Not evaluated
Other; specify: ___________	☐ Absent ☐ Present

ACUTE LEUKAEMIAS
Acute Myeloid Leukaemias (AML) - *main disease code 1*

MOLECULAR MARKER ANALYSIS

Molecular Marker analysis at diagnosis:

☐ Absent
☐ Present
☐ Not done or failed
☐ Unknown

Indicate below whether the markers were absent, present or not evaluated.

AML1-ETO (RUNX1/RUNXT1) *Molecular product of t(8;21)*	☐ Absent	☐ Present	☐ Not evaluated
CBFB-MYH11 *Molecular product of inv(16)(p13.1;q22) or (16;16)(p13.1;q22)*	☐ Absent	☐ Present	☐ Not evaluated
PML-RARα *Molecular product of t(15;17)*	☐ Absent	☐ Present	☐ Not evaluated
MLL-rearrangement/mutation *(fill in only if 11q23 abnormality is present)*:	☐ Absent	☐ Present	☐ Not evaluated
MLLT3(AF9)-MLL *Molecular product of t(9;11)(p22;q23)*	☐ Absent	☐ Present	☐ Not evaluated
MLL-PTD (partial tandem duplication)	☐ Absent	☐ Present	☐ Not evaluated
MLLT4(AF6)-MLL *Molecular product of t(6;11)(q27;q23)*	☐ Absent	☐ Present	☐ Not evaluated
ELL-MLL *Molecular product of t(11;19)(q23;p13.1)*	☐ Absent	☐ Present	☐ Not evaluated
MLLT1(ENL)-MLL *Molecular product of t(11;19)(q23;p13.3)*	☐ Absent	☐ Present	☐ Not evaluated
MLLT10(AF10)-MLL *Molecular product of t(10;11)(p12;q23)*	☐ Absent	☐ Present	☐ Not evaluated
Other MLL-rearrangement; specify: _____	☐ Absent	☐ Present	☐ Not evaluated
DEK-NUP214(CAN) *Molecular product of translocation t(6;9)(p23;q34)*	☐ Absent	☐ Present	☐ Not evaluated
RPN1-EVI1 *Molecular product of inv(3)(q21q26.2) or t(3;3)(q21q26.2)*	☐ Absent	☐ Present	☐ Not evaluated
RBM15-MKL1 *Molecular product of translocation t(1;22)(p13;q13)*	☐ Absent	☐ Present	☐ Not evaluated
NPM1 mutation	☐ Absent	☐ Present	☐ Not evaluated
CEBPA mutation	☐ Absent	☐ Present	☐ Not evaluated
FLT3-ITD (internal tandem duplication)	☐ Absent	☐ Present	☐ Not evaluated
DNMT3A	☐ Absent	☐ Present	☐ Not evaluated
ASXL1	☐ Absent	☐ Present	☐ Not evaluated
TP53	☐ Absent	☐ Present	☐ Not evaluated
RUNX1	☐ Absent	☐ Present	☐ Not evaluated
c-KIT	☐ Absent	☐ Present	☐ Not evaluated
Other; specify: _____	☐ Absent	☐ Present	☐ Not evaluated

ACUTE LEUKAEMIAS
Acute Myeloid Leukaemias (AML) - *main disease code 1*

INVOLVEMENT AT DIAGNOSIS

Involvement at diagnosis:

Bone Marrow:	☐ No	☐ Yes	☐ Not evaluated
CNS:	☐ No	☐ Yes	☐ Not evaluated
Testes/Ovary:	☐ No	☐ Yes	☐ Not evaluated
Other:	☐ No	☐ Yes; specify: _____	

ACUTE LEUKAEMIAS
Precursor Lymphoid Neoplasms (previously ALL) - *main disease code 1*

DISEASE

Classification:

- ☐ B lymphoblastic leukaemia/lymphoma *(previously Precursor B-cell ALL)*
  - ☐ with t(9;22)(q34;q11.2); BCR-ABL1
  - ☐ with t(v;11q23); MLL rearranged
  - ☐ with t(1;19)(q23;p13.3); E2A-PBX1
  - ☐ with t(12;21)(p13;q22); TEL-AML1 (ETV-RUNX1)
  - ☐ with hyperdiploidy
  - ☐ with hypodiploidy
  - ☐ with t(5;14)(q31;q32); IL3-IGH
  - ☐ Not otherwise specified (NOS)
  - ☐ Other; specify: _____
- ☐ T Lymphoblastic Leukaemia/Lymphoma *(previously Precursor T-cell ALL)*

Secondary origin: Is this PLN related to prior exposure of therapeutic drugs or radiation?

☐ No
☐ Yes
☐ Unknown

Is this a donor cell leukaemia?
(Only applicable if the patient has received an allograft prior to the diagnosis of acute leukaemia.)

☐ No
☐ Yes
☐ Not evaluated

CHROMOSOME ANALYSIS

Chromosome analysis at diagnosis *(all methods including FISH)*:
(Include all analyses <u>before</u> treatment; describe results of the most recent complete analysis)

☐ Normal		
☐ Abnormal:	Complex karyotype: *(3 or more abnormalities)*	☐ No ☐ Yes ☐ Unknown
☐ Not done or failed		
☐ Unknown		

ACUTE LEUKAEMIAS
Precursor Lymphoid Neoplasms (previously ALL) **-** *main disease code 1*

CHROMOSOME ANALYSIS continued

Transcribe the complete karyotype: ____

OR

Indicate below whether the abnormalities were absent, present or not evaluated.

t(9;22)	☐ Absent	☐ Present	☐ Not evaluated
11q23 abnormalities *(fill in only if 11q23 abnormalities is present)*	☐ Absent	☐ Present	☐ Not evaluated
t(4;11)	☐ Absent	☐ Present	☐ Not evaluated
Other abn(11q23); specify: ____________________	☐ Absent	☐ Present	
t(12;21)	☐ Absent	☐ Present	☐ Not evaluated
Hyperdiploidy (>46 chromosomes) *(fill in only if hyperdiploidy is present)*:	☐ Absent	☐ Present	☐ Not evaluated
50 – 66 chromosomes	☐ Absent	☐ Present	☐ Not evaluated
Trisomy; specify extra chromosome: _____	☐ Absent	☐ Present	☐ Not evaluated
Other hyperdiploid karyotype; number of chromosomes: _____	☐ Absent	☐ Present	
Hypodiploidy (<46 chromosomes): *(fill in only if hypodiploidy is present)*:	☐ Absent	☐ Present	☐ Not evaluated
Low hypodiploid; 32 - 39 chromosomes;	☐ Absent	☐ Present	☐ Not evaluated
Near haploid, 24-31 chromosomes;	☐ Absent	☐ Present	☐ Not evaluated
Monosomy; specify: ____________________	☐ Absent	☐ Present	☐ Not evaluated
Other; number of chromosomes: _____	☐ Absent	☐ Present	
t(5;14)(q31;q32)	☐ Absent	☐ Present	☐ Not evaluated
t(1;19)	☐ Absent	☐ Present	☐ Not evaluated
Trisomy 8	☐ Absent	☐ Present	☐ Not evaluated
Other; specify: ____________________	☐ Absent	☐ Present	

MOLECULAR MARKER ANALYSIS

Molecular Marker analysis at diagnosis:

☐ Absent
☐ Present
☐ Not done or failed
☐ Unknown

ACUTE LEUKAEMIAS
Precursor Lymphoid Neoplasms (previously ALL) - *main disease code 1*

MOLECULAR MARKER ANALYSIS continued

Indicate below whether the abnormalities were absent, present or not evaluated.

BCR-ABL *Molecular product of t(9;22)(q34;q11.2)*	☐ Absent	☐ Present	☐ Not evaluated
MLL-rearrangement/mutation *(fill in only if a MLL-rearrangement abnormality is present)*:	☐ Absent	☐ Present	☐ Not evaluated
AFF1(AF4)-MLL *Molecular product of t(4;11)(q21;q23)*	☐ Absent	☐ Present	☐ Not evaluated
MLLT1(ENL)-MLL *Molecular product of t(11;19)(q23;p13.3)*	☐ Absent	☐ Present	☐ Not evaluated
MLLT3(AF9)-MLL *Molecular product of t(9;11)(p22;q23)*	☐ Absent	☐ Present	☐ Not evaluated
Other MLL-rearrangement; specify: _____	☐ Absent	☐ Present	
TEL(ETV6)-AML1(RUNX1) *Molecular product of t(12;21)(p13;q22)*	☐ Absent	☐ Present	☐ Not evaluated
IL3-IGH *Molecular product of translocation t(5;14)(q31;q32)*	☐ Absent	☐ Present	☐ Not evaluated
TCF3-PBX1 *Molecular product of translocation (1;19)(q23;p13.3)*	☐ Absent	☐ Present	☐ Not evaluated
IKZF1 (IKAROS)	☐ Absent	☐ Present	☐ Not evaluated
NOTCH1 & FBWX7	☐ Absent	☐ Present	☐ Not evaluated
Other; specify: _____	☐ Absent	☐ Present	

White blood cell count at diagnosis: _____ 10^9 cells/L ☐ Not available/Unknown

ACUTE LEUKAEMIAS
Other Acute Leukaemias - *main disease code 1*

DISEASE

Classification:

Acute leukaemia of ambiguous lineage

- ☐ Acute undifferentiated leukaemia
- ☐ Mixed phenotype NOS
  - ☐ Mixed phenotype B/myeloid, NOS
  - ☐ Mixed phenotype T/myeloid, NOS
- ☐ Natural killer (NK) - cell lymphoblastic leukaemia/lymphoma
- ☐ Other: specify: _____

Secondary origin: Is this other acute leukaemia related to prior exposure of therapeutic drugs or radiation?

☐ No
☐ Yes
☐ Unknown

Is this a donor cell leukaemia?
(Only applicable if the patient has received an allograft prior to the diagnosis of acute leukaemia.)

☐ No
☐ Yes
☐ Not evaluated

CHRONIC LEUKAEMIAS
Chronic Myelogenous Leukaemias (CML) - *main disease code 2*

DISEASE

Classification:
(At least one investigation must be positive; note: CMML is not a CML but MDS/MPN.)

t(9;22) *(Chromosome analysis)*	☐ Absent	☐ Present	☐ Not evaluated
bcr-abl *(Molecular marker analysis)*	☐ Absent	☐ Present	☐ Not evaluated

CHRONIC LEUKAEMIAS
Chronic Lymphocytic Leukaemias (CLL) - *main disease code 2*

DISEASE

Classification:

☐ Chronic lymphocytic leukaemia (CLL) / small lymphocytic lymphoma

☐ Richter's syndrom:

Transformed from a previous known CLL? ☐ Yes: Date of original CLL diagnosis: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*
☐ No: Primary Richter *(without previously known diagnosis of CLL)*

CHROMOSOME ANALYSIS

Chromosome analysis at diagnosis *(all methods including FISH)***:**
(Include all analyses before treatment; describe results of the most recent complete analysis)

☐ Normal
☐ Abnormal
☐ Not done or failed
☐ Unknown

Transcribe the complete karyotype: ____

OR

Indicate below whether the abnormalities were absent, present or not evaluated.

Trisomy 12	☐ Absent	☐ Present	☐ Not evaluated
del(13q14)	☐ Absent	☐ Present	☐ Not evaluated
del(11q22-23)	☐ Absent	☐ Present	☐ Not evaluated
del(17p)	☐ Absent	☐ Present	☐ Not evaluated
Other; specify: ________________	☐ Absent	☐ Present	

CHRONIC LEUKAEMIAS
Chronic Lymphocytic Leukaemias (CLL) - *main disease code 2*

MOLECULAR MARKER ANALYSIS

Molecular Marker analysis at diagnosis:

☐ Absent
☐ Present
☐ Not done of failed
☐ Unknown

Indicate below whether the markers were absent, present or not evaluated.

TP53 mutations	☐ Absent ☐ Present ☐ Not evaluated
Other; specify: _____	☐ Absent ☐ Present

CHRONIC LEUKAEMIAS
Prolymphocytic Leukaemias (PLL) and Others - *main disease code 2*

DISEASE

Classification:

☐ Prolymphocytic Leukaemia (PLL)
- ☐ PLL; B-cell
- ☐ PLL; T-cell

☐ Hairy Cell Leukaemia

☐ Other chronic leukaemia; specify: _____

CHROMOSOME ANALYSIS
only applicable for PLL

Chromosome analysis at diagnosis *(all methods including FISH)*:
(Include all analyses before treatment; describe results of the most recent complete analysis)

☐ Normal
☐ Abnormal
☐ Not done or failed
☐ Unknown

CHRONIC LEUKAEMIAS
Prolymphocytic Leukaemias (PLL) and Others - *main disease code 2*

CHROMOSOME ANALYSIS continued

only applicable for PLL

Transcribe the complete karyotype: ____

OR

Indicate below whether the abnormalities were absent, present or not evaluated.

inv(14)/ t(14;14)(q11;q32)	☐ Absent ☐ Present ☐ Not evaluated
del(14)(q12)	☐ Absent ☐ Present ☐ Not evaluated
t(11;14)(q23;q11)	☐ Absent ☐ Present ☐ Not evaluated
t(7;14)(q35;q32.1)	☐ Absent ☐ Present ☐ Not evaluated
t(X;14)(q35;q11)	☐ Absent ☐ Present ☐ Not evaluated
idic(8)(p11)	☐ Absent ☐ Present ☐ Not evaluated
Other; specify: _______________	☐ Absent ☐ Present

IMMUNOPHENOTYPING

only applicable for T-cell PLL

Immunophenotype of T-cells at diagnosis:
Note: Terminal desoxynucleotidyl transferase (TdT) must be negative.

Indicate below whether the phenotypes were absent, present or not evaluated.

CD4+	☐ Absent ☐ Present ☐ Not evaluated
CD8+	☐ Absent ☐ Present ☐ Not evaluated

Lymphocyte count at diagnosis: _______________ 10^9 cells/L

LYMPHOMAS
B-Cell Non-Hodgkin Lymphomas (NHL) - *main disease code 3*

DISEASE

Classification: Mature B-cell Neoplasms

☐ Splenic marginal zone lymphoma	
☐ Extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT)	
☐ Nodal marginal zone lymphoma	
☐ Lymphoplasmacytic lymphoma (LPL)	
☐ Waldenstrom macroglobulinaemia (LPL with monoclonal IgM)	**International Prognostic Scoring System for Waldenström's Macroglobulinemia (ISSWM):** ☐ Low risk *(0-1 score points except age >65)* ☐ Intermediate risk *(2 score points or age >65 alone)* ☐ High risk *(3-5 score points)* ☐ Not evaluated
☐ Follicular lymphoma	**Grading:** ☐ Grade I ☐ Grade II ☐ Grade III ☐ Not evaluated **Prognostic score (FLIPI):** ☐ Low risk ☐ Intermediate risk ☐ High risk ☐ Not evaluated
☐ Primary cutaneous follicle centre lymphoma	
☐ Mantle cell lymphoma	**Grading:** ☐ Indolent ☐ Classical ☐ Pleomorphic ☐ Blastoid ☐ Not evaluated **Prognostic score (MIPI):** ☐ Low risk ☐ Intermediate risk ☐ High risk ☐ Not evaluated **KI-67 *(proliferation index)*: _ _ % positive** ☐ Not evaluated
☐ Diffuse large B-cell lymphoma (DLBCL), (NOS)	**International prognostic score (IPI):** ☐ Low risk *(0-1 score points)* ☐ Low-intermediate risk *(2 score points)* ☐ High-intermediate risk *(3 score points)* ☐ High risk *(4-5 score points)* ☐ Not evaluated **KI-67: _ _ % positive *(proliferation index)*** ☐ Not evaluated
☐ T-cell/histiocyte rich large B cell lymphoma	
☐ Primary DLBCL of the CNS	
☐ Primary cutaneous DLBCL, leg type	
☐ EBV positive DLBCL of the elderly	
☐ Germinal centre B-cell type (GCB) DLBCL	
☐ Activated B-cell type (ABC or non-GCB) DLBCL	
☐ DLBCL associated with chronic inflammation	
☐ Lymphomatoid granulomatosis	
☐ Primary mediastinal (thymic) large B-cell lymphoma	
☐ Intravascular large B-cell lymphoma	
☐ ALK-positive large B-cell lymphoma	
☐ Plasmablastic lymphoma	
☐ HHV8-positive DLBCL,NOS	
☐ Primary effusion lymphoma (PEL)	
☐ Burkitt lymphoma (BL)	
☐ High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements	
☐ B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma (Intermediate DLCBL/BL)	
☐ B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (Gray zone lymphoma)	
☐ Other B-cell lymphoma; specify: _____	

LYMPHOMAS
B-Cell Non-Hodgkin Lymphomas (NHL) - *main disease code 3*

DISEASE continued

Transformed from another type of lymphoma at the event leading to this cellular therapy?

☐ No

☐ Yes: Date of original diagnosis: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Indicate the type of the original lymphoma: _____

☐ Unknown

Please complete Chromosome Analysis, Molecular Marker Analysis and Immunophenotyping sections only for patients receiving cellular therapy for the followin types of B-cell NHL:

- *Mantle cell lymphoma*
- *Waldenstrom macroglobulinaemia*
- *Burkitt lymphoma or Intermediate DLBCL/ Burkitt lymphoma*

CHROMOSOME ANALYSIS

Chromosome analysis at diagnosis *(all methods including FISH)*:
(Include all analyses before treatment; describe results of the most recent complete analysis)

☐ Normal

☐ Abnormal

☐ Not done or failed

☐ Unknown

If abnormal, complete this table according to the type of lymphoma diagnosed.

Mantle cell lymphoma or Waldenstrom macro- globulinaemia	**del(17p)** FISH used: ☐ No ☐ Yes	☐ Absent ☐ Present ☐ Not evaluated
Burkitt lymphoma or Intermediate DLBCL/ Burkitt lymphoma	**t(2;8)**	☐ Absent ☐ Present ☐ Not evaluated
	t(8;14)	☐ Absent ☐ Present ☐ Not evaluated
	t(8;22)	☐ Absent ☐ Present ☐ Not evaluated
	t(14;18)	☐ Absent ☐ Present ☐ Not evaluated
	myc rearrangement	☐ Absent ☐ Present ☐ Not evaluated
	BCL2 rearrangement	☐ Absent ☐ Present ☐ Not evaluated
	BCL6 rearrangement	☐ Absent ☐ Present ☐ Not evaluated

LYMPHOMAS
B-Cell Non-Hodgkin Lymphomas (NHL) - *main disease code 3*

Please complete Chromosome Analysis, Molecular Marker Analysis and Immunophenotyping sections only for patients receiving cellular therapy for the followin types of B-cell NHL:

- *Mantle cell lymphoma*
- *Waldenstrom macroglobulinaemia*
- *Burkitt lymphoma or Intermediate DLBCL/ Burkitt lymphoma*

MOLECULAR MARKER ANALYSIS

Molecular Marker analysis at diagnosis:

☐ Absent
☐ Present
☐ Not done of failed
☐ Unknown

If abnormal, complete this table according to the type of lymphoma diagnosed.

Mantle cell lymphoma	**TP53 mutation**	☐ Absent ☐ Present ☐ Not evaluated
Burkitt lymphoma or Intermediate DLBCL/ Burkitt lymphoma	**myc rearrangment**	☐ Absent ☐ Present ☐ Not evaluated
Intermediate DLBCL/ Burkitt lymphoma	**BCL2 rearrangement**	☐ Absent ☐ Present ☐ Not evaluated
	BCL6 rearrangement	☐ Absent ☐ Present ☐ Not evaluated

IMMUNOPHENOTYPING

Immunophenotyping at diagnosis:

☐ Absent
☐ Present
☐ Not done of failed
☐ Unknown

If abnormal, complete this table according to the type of lymphoma diagnosed.

Mantle cell lymphoma	**SOX 11**	☐ Absent ☐ Present ☐ Not evaluated
Burkitt lymphoma or Intermediate DLBCL/ Burkitt lymphoma	**MYC**	☐ Absent ☐ Present ☐ Not evaluated
Intermediate DLBCL/ Burkitt lymphoma	**BCL2/IgH**	☐ Absent ☐ Present ☐ Not evaluated
	BCL6	☐ Absent ☐ Present ☐ Not evaluated

LYMPHOMAS
T-Cell Non-Hodgkin Lymphomas (NHL) - *main disease code 3*

DISEASE

Classification: Mature T-cell & NK-cell Neoplasms

☐ T-cell large granular lymphocytic leukaemia	
☐ Aggressive NK-cell leukaemia	
☐ Systemic EBV positive T-cell lymphoproliferative disease of childhood	
☐ Hydroa vacciniforme-like lymphoma	
☐ Adult T-cell leukaemia/lymphoma	
☐ Extranodal NK/T-cell lymphoma, nasal type	
☐ Enteropathy-associated T-cell lymphoma	
☐ Monomorphic epitheliotropic intestinal T-cell lymphoma	
☐ Hepatosplenic T-cell lymphoma	
☐ Subcutaneous panniculitis-like T-cell lymphoma	
☐ Mycosis fungoides (MF)	**ISCL/EORT staging:** ☐ IA ☐ IIIA ☐ IVB ☐ IB ☐ IIIB ☐ Not evaluated ☐ IIA ☐ IVA1 ☐ IIB ☐ IVA2
☐ Sézary syndrome	
☐ Lymphomatoid papulosis	
☐ Primary cutaneous anaplastic large cell lymphoma	
☐ Primary cutaneous gamma-delta T-cell lymphoma	
☐ Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma	
☐ Primary cutaneous CD4 positive small/medium T-cell lymphoma	
☐ Peripheral T-cell lymphoma NOS (PTCL)	**International prognostic score (IPI):** ☐ Low risk *(0-1 score points)* ☐ Low-intermediate risk *(2 score points)* ☐ High-intermediate risk *(3 score points)* ☐ High risk *(4-5 score points)* ☐ Not evaluated
☐ Angioimmunoblastic T-cell lymphoma	
☐ Anaplastic large-cell lymphoma (ALCL), ALK-positive	
☐ Anaplastic large-cell lymphoma (ALCL), ALK-negative	
☐ Other T-cell: specify: _____	

LYMPHOMAS
Hodgkin Lymphomas - *main disease code 3*

DISEASE

Classification:

- ☐ Nodular lymphocyte predominant
- ☐ Classical predominant; lymphocyte-rich
- ☐ Classical predominant; nodular sclerosis
- ☐ Classical predominant; mixed cellularity
- ☐ Classical predominant; lymphocyte-depleted
- ☐ Classical predominant; NOS
- ☐ Other; specify: _____

LYMPHOMAS
Immunodeficiency-associated lymphoproliferative disorders (incl. PTLD) - *main disease code 3*

DISEASE

Classification:

- ☐ Lymphoproliferative disease associated with primary immune disorder
- ☐ Lymphoma associated with HIV infection
- ☐ Post-transplant lymphoproliferative disorder (PTLD)
  - ☐ Non-destructive PTLD
    - ☐ Plasmacytic hyperplasia PTLD
    - ☐ Infectious mononucleosis PTLD
    - ☐ Florid follicular hyperplasia PTLD
  - ☐ Polymorphic PTLD
  - ☐ Monomorphic PTLD
    - ☐ B-cell type
    - ☐ T-/NK-cell type
  - ☐ Classical Hodgkin lymphoma PTLD
- ☐ Other iatrogenic immunodeficiency-associated lymphoproliferative disorder

Did the disease result from a previous solid organ transplant?

☐ No

☐ Yes: Date of transplant: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Type of transplant:
- ☐ Renal
- ☐ Cardiac
- ☐ Pulmonary
- ☐ Other; specify: _____

☐ Unknown

MYELODYSPLASTIC SYNDROMES (MDS)
main disease code 6

DISEASE

Classification:

- ☐ Refractory anaemia without ring sideroblasts (RA)
- ☐ Refractory anaemia with ring sideroblasts (RARS)
- ☐ Myelodysplastic syndrome with isolated del(5q) chromosomal abnormality
- ☐ Refractory cytopenia with multi-lineage dysplasia (RCMD)
- ☐ Refractory cytopenia with multi-lineage dysplasia with ringed sideroblasts (RCMD-RS)
- ☐ Refractory anaemia with excess of blasts-1 (RAEB-1)
- ☐ Refractory anaemia with excess of blasts-2 (RAEB-2)
- ☐ Childhood myelodysplastic syndrome (Refractory cytopenia of childhood; RCC)
- ☐ Myelodysplastic syndrome, unclassifiable (MDS-U)

Therapy-related MDS?
(Secondary origin)

- ☐ No
- ☐ Yes, disease related to prior exposure to therapeutic drugs or radiation
- ☐ Unknown

Is this a donor cell leukaemia?
(Only applicable if the patient has received an allograft prior to the diagnosis of MDS.)

- ☐ No
- ☐ Yes
- ☐ Not evaluated

CHROMOSOME ANALYSIS

Chromosome analysis at diagnosis *(all methods including FISH)*:
(Include all analyses before treatment; describe results of the most recent complete analysis)

- ☐ Normal
- ☐ Abnormal: Complex karyotype: *(3 or more abnormalities)* ☐ No ☐ Yes ☐ Unknown
- ☐ Not done or failed
- ☐ Unknown

MYELODYSPLASTIC SYNDROMES (MDS)

main disease code 6

CHROMOSOME ANALYSIS continued

Transcribe the complete karyotype: ____

OR

Indicate below whether the abnormalities were absent, present or not evaluated.

del(Y)	☐ Absent	☐ Present	☐ Not evaluated
abn 5 type *(fill in only if an abn 5 is present)*:	☐ Absent	☐ Present	☐ Not evaluated
del(5q)	☐ Absent	☐ Present	☐ Not evaluated
Other abn(5q); specify: __________	☐ Absent	☐ Present	
del(20q)	☐ Absent	☐ Present	☐ Not evaluated
abn 7 type *(Ffll in only if an abn 7 is present)*:	☐ Absent	☐ Present	☐ Not evaluated
del(7q)	☐ Absent	☐ Present	☐ Not evaluated
Other abn(7q); specify: __________	☐ Absent	☐ Present	
abn 3 type *(Ffll in only if an abn 3 is present)*:	☐ Absent	☐ Present	☐ Not evaluated
inv(3)	☐ Absent	☐ Present	☐ Not evaluated
t(3q;3q)	☐ Absent	☐ Present	☐ Not evaluated
del(3q)	☐ Absent	☐ Present	☐ Not evaluated
Other abn(3q); specify: _________	☐ Absent	☐ Present	
del(11q)	☐ Absent	☐ Present	☐ Not evaluated
Trisomy 8	☐ Absent	☐ Present	☐ Not evaluated
Trisomy 19	☐ Absent	☐ Present	☐ Not evaluated
i(17q)	☐ Absent	☐ Present	☐ Not evaluated
Other; specify: ___________	☐ Absent	☐ Present	

MOLECULAR MARKER ANALYSIS

Molecular Marker analysis at diagnosis:

☐ Absent

☐ Present

☐ Not done or fialed

☐ Unknown

If an AML with myelodysplasia-related changes is entered, return to Acute Leukaemias on page 8 to continue.

COMBINED MYELODYSPLASTIC SYNDROME/MYELOPROLIFERATIVE NEOPLASM (MDS/MPN) - *main disease code 6*

DISEASE

Classification:

☐ Chronic myelomonocytic leukaemia (CMMoL, CMML)
☐ Juvenile myelomonocytic leukaemia (JCMMoL, JMML, JCML, JCMML)
☐ Atypical CML (t(9;22) negative and BCR-ABL1 negative)

Therapy-related MDS/MPD?
(Secondary origin)

☐ No

☐ Yes, disease related to prior exposure to therapeutic drugs or radiation

☐ Unknown

CHROMOSOME ANALYSIS

Chromosome analysis at diagnosis *(all methods including FISH)***:**
(Include all analyses before treatment; describe results of the most recent complete analysis)

☐ Normal		
☐ Abnormal:	Complex karyotype: *(3 or more abnormalities)*	☐ No ☐ Yes ☐ Unknown
☐ Not done or failed		
☐ Unknown		

Transcribe the complete karyotype: ____

OR

Indicate below whether the abnormalities were absent, present or not evaluated.

abn 1 type; specify: _______________	☐ Absent	☐ Present	☐ Not evaluated
abn 5 type; specify: _______________	☐ Absent	☐ Present	☐ Not evaluated
abn 7 type; specify: _______________	☐ Absent	☐ Present	☐ Not evaluated
Trisomy 8	☐ Absent	☐ Present	☐ Not evaluated
Trisomy 9	☐ Absent	☐ Present	☐ Not evaluated
del(20q)	☐ Absent	☐ Present	☐ Not evaluated
del(13q)	☐ Absent	☐ Present	☐ Not evaluated
Other; specify: _______________	☐ Absent	☐ Present	

COMBINED MYELODYSPLASTIC SYNDROME/MYELOPROLIFERATIVE NEOPLASM (MDS/MPN) - *main disease code 6*

MOLECULAR MARKER ANALYSIS

Molecular Marker analysis at diagnosis:

☐ Absent
☐ Present
☐ Not done or failed
☐ Unknown

Indicate below whether the markers were absent, present or not evaluated.

BCR-ABL; *Molecular product of t(9;22)(q34;q11.2)*	☐ Absent	☐ Present	☐ Not evaluated
JAK2 mutation	☐ Absent	☐ Present	☐ Not evaluated
FIP1L1-PDGFR	☐ Absent	☐ Present	☐ Not evaluated
PTPN-11	☐ Absent	☐ Present	☐ Not evaluated
K-RAS	☐ Absent	☐ Present	☐ Not evaluated
N-RAS	☐ Absent	☐ Present	☐ Not evaluated
CBL	☐ Absent	☐ Present	☐ Not evaluated
Other; specify: _____	☐ Absent	☐ Present	

MYELOPROLIFERATIVE NEOPLASM (MPN)
main disease code 6

DISEASE

Classification:

☐ Primary myelofibrosis (Chronic idiopathic myelofibrosis; fibrosis with myeloid metaplasia)
☐ Polycythaemia vera
☐ Essential or primary thrombocythaemia
☐ Hyper eosinophilic syndrome (HES)
☐ Chronic eosinophilic leukaemia (CEL)
☐ Chronic neutrophilic leukaemia
☐ Systemic mastocytosis
☐ Mast cell leukaemia
☐ Mast cell sarcoma
☐ MPN not otherwise specified
☐ Myeloid and lymphoid neoplasms with FGFR1 abnormalities (Stem cell leukaemia-lymphoma syndrome, 8p11 syndrome)
☐ Other; specify: _____

Therapy-related MDS/MPD?
(Secondary origin)

☐ No

☐ Yes, disease related to prior exposure to therapeutic drugs or radiation

☐ Unknown

IPPS risk score for myelofibrosis:

☐ Low risk

☐ Intermediate-1

☐ Intermediate-2

☐ High risk

☐ Not evaluated

MYELOPROLIFERATIVE NEOPLASM (MPN)

main disease code 6

CHROMOSOME ANALYSIS

Chromosome analysis at diagnosis *(all methods including FISH)*:
(Include all analyses before treatment; describe results of the most recent complete analysis)

☐ Normal		
☐ Abnormal:	Complex karyotype: *(3 or more abnormalities)*	☐ No ☐ Yes ☐ Unknown
☐ Not done or failed		
☐ Unknown		

Transcribe the complete karyotype: ____

OR

Indicate below whether the abnormalities were absent, present or not evaluated.

abn 1 type; specify: _______________	☐ Absent	☐ Present	☐ Not evaluated
abn 5 type; specify: _______________	☐ Absent	☐ Present	☐ Not evaluated
abn 7 type; specify: _______________	☐ Absent	☐ Present	☐ Not evaluated
Trisomy 8	☐ Absent	☐ Present	☐ Not evaluated
Trisomy 9	☐ Absent	☐ Present	☐ Not evaluated
del(20q)	☐ Absent	☐ Present	☐ Not evaluated
del(13q)	☐ Absent	☐ Present	☐ Not evaluated
Other; specify: _______________	☐ Absent	☐ Present	

MOLECULAR MARKER ANALYSIS

Molecular Marker analysis at diagnosis:

☐ Absent
☐ Present
☐ Not done or failed
☐ Unknown

MYELOPROLIFERATIVE NEOPLASM (MPN)

main disease code 6

MOLECULAR MARKER ANALYSIS continued

Indicate below whether the markers were absent, present or not evaluated.

BCR-ABL; *Molecular product of t(9;22)(q34;q11.2)*	☐ Absent ☐ Present ☐ Not evaluated
JAK2 mutation	☐ Absent ☐ Present ☐ Not evaluated **If present: allele burden _____ %**
cMPL mutation	☐ Absent ☐ Present ☐ Not evaluated
Calreticulin (CALR) mutation	☐ Absent ☐ Present ☐ Not evaluated
FIP1L1-PDGFR	☐ Absent ☐ Present ☐ Not evaluated
Other; specify: _____	☐ Absent ☐ Present

PLASMA CELL DISORDERS (PCD) incl. MULTIPLE MYELOMA (MM)
main disease code 4

DISEASE

Classification:

☐ Multiple myeloma (MM)		Heavy chain type:	Light chain type:
☐ MM; heavy chain and light chain	→ *Check light and/or heavy chain types as applicable*	☐ IgG ☐ IgA ☐ IgD ☐ IgE ☐ IgM (not Waldenstrom)	☐ Kappa ☐ Lambda
☐ MM; light chain	→		
☐ MM; non-secretory			
☐ Plasma cell leukaemia			
☐ Solitary plasmacytoma of bone			
☐ Primary amyloidosis			
☐ POEMS			
☐ Monoclonal light and heavy chain deposition disease (LCDD/HCDD)			
☐ Other; specify: _____			

Staging at diagnosis:

Salmon & Durie staging for multiple myeloma:
(Please tick both columns.)

Stage	Symptoms
☐ I	☐ A
☐ II	☐ B
☐ II	

Revised ISS:

Stage
☐ I: ISSI I without high risk FISH and normal LDH
☐ II: not R-ISS I or III
☐ III: any ISS with high risk FISH and/or high LDH

OR

ISS STAGE:

Stage	β2-µglob (mg/L)	Albumin (g/L)
☐ I	< 3.5	> 35
☐ II	< 3.5	< 35
OR	3.5 ≤ 5.5	any
☐ III	> 5.5	any

PLASMA CELL DISORDERS (PCD) incl. MULTIPLE MYELOMA (MM)

main disease code 4

CHROMOSOME ANALYSIS

Not applicable for Primary amyloidosis.

Chromosome analysis at diagnosis *(all methods including FISH)***:**
(Include all analyses before treatment; describe results of the most recent complete analysis)

☐ Normal		
☐ Abnormal:	Complex karyotype: *(3 or more abnormalities)*	☐ No ☐ Yes ☐ Unknown
☐ Not done or failed		
☐ Unknown		

Transcribe the complete karyotype: ____

OR

Indicate below whether the abnormalities were absent, present or not evaluated.

del(13q14)	☐ Absent	☐ Present	☐ Not evaluated
t(11;14)	☐ Absent	☐ Present	☐ Not evaluated
abn(17q)	☐ Absent	☐ Present	☐ Not evaluated
del(17p)	☐ Absent	☐ Present	☐ Not evaluated
t(4:14)	☐ Absent	☐ Present	☐ Not evaluated
t(14:16)	☐ Absent	☐ Present	☐ Not evaluated
1q amplification	☐ Absent	☐ Present	☐ Not evaluated
myc rearrangement	☐ Absent	☐ Present	☐ Not evaluated
Other; specify: ________________	☐ Absent	☐ Present	

MOLECULAR MARKER ANALYSIS

Not applicable for Primary amyloidosis.

Molecular Marker analysis at diagnosis:

☐ Absent
☐ Present
☐ Not done or failed
☐ Unknown

BONE MARROW FAILURE SYNDROMES (BMF) incl. APLASTIC ANAEMIA (AA)

main disease code 7

DISEASE

Classification:

Aquired:

☐ Severe Aplastic Anaemia (SAA)	Etiology:
☐ Amegakaryocytosis, acquired (not congenital)	☐ Secondary to hepatitis
☐ Acquired Pure Red Cell Aplasia (PRCA) (not congenital)	☐ Secondary to toxin/other drug
☐ Paroxysmal nocturnal haemoglobinuria (PNH)	☐ Idiopathic
☐ Acquired Pure White Cell Aplasia	☐ Other; specify: _____
☐ Other acquired cytopenic syndrome; specify: _____	

Congenital:

☐ Amegakaryocytosis / thrombocytopenia
☐ Fanconi anaemia
☐ Diamond-Blackfan anaemia (congenital PRCA)
☐ Shwachman-Diamond Syndrome
☐ Dyserythropoietic anaemia
☐ Dyskeratoris congenita
☐ Other congenital anaemia; specify: _____

HAEMOGLOBINOPATHY
main disease code 1

DISEASE

Classification:

☐ Thalassaemia
- ☐ Beta 0
- ☐ Beta+
- ☐ Beta E
- ☐ Beta S (sickle cell + thalassaemia): **Percentage sickle cell:** _____ %

☐ Sickle Cell Disease

☐ Other haemoglobinopathy; specify: _____

SOLID TUMOURS
main disease code 5

DISEASE

Classification:

- ☐ Bone sarcoma (excluding Ewing sarcoma/PNET)
- ☐ Breast
- ☐ Central nervous system tumours (include CNS PNET)
- ☐ Colorectal
- ☐ Ewing sarcoma (ES)/PNET, extra-skeletal
- ☐ Ewing sarcoma(ES)/PNET, skeletal
- ☐ Germ cell tumour, extragonadal only
- ☐ Germ cell tumour, gonadal
- ☐ Head and neck
- ☐ Hepatobiliary
- ☐ Kidney cancer excluding Wilm's tumour
- ☐ Lung cancer, non-small cell
- ☐ Lung cancer, small cell
- ☐ Medulloblastoma
- ☐ Melanoma
- ☐ Neuroblastoma
- ☐ Ovarian (carcinoma)
- ☐ Pancreatic
- ☐ Prostate
- ☐ Renal cell
- ☐ Retinoblastoma
- ☐ Rhabdomyosarcoma
- ☐ Soft tissue sarcoma (excluding Rhabdo. and extra-skeletal ES)
- ☐ Thymoma
- ☐ Wilm's tumour
- ☐ Other; specify: _____

TNM classification:

Type:
- ☐ Clinical
- ☐ Pathological

Tumour:
- ☐ TX
- ☐ T0
- ☐ T1
- ☐ T2
- ☐ T3
- ☐ T4
- ☐ Not evaluated
- ☐ Unknown

Nodes:
- ☐ NX
- ☐ N0
- ☐ N1
- ☐ N2
- ☐ N3
- ☐ Not evaluated
- ☐ Unknown

Metastases:
- ☐ MX
- ☐ M0
- ☐ M1
- ☐ Not evaluated
- ☐ Unknown

SOLID TUMOURS
main disease code 5

DISEASE continued

Disease-specific staging:

☐ I
☐ II
☐ III
☐ IV
☐ Not evaluated
☐ Unknown

Breast carcinoma risk factors and staging at diagnosis *(Breast carcinoma only)*:

Receptor status:

Estrogen (ER): ☐ Negative ☐ Positive: ER values: _____ ☐ Not evaluated
Progesteron (PgR): ☐ Negative ☐ Positive: PgR values: _____ ☐ Not evaluated
HER2/neu (c-erb-B2): ☐ Negative ☐ Positive ☐ Not evaluated

Defined by: ☐ ICH 3+ ☐ IHC 1/2+ and FISH+

Axillary lymph nodes at surgery: Nº positive / Nº examined = _____ / _____ ☐ Not evaluated

Sentinel Node: ☐ Negative ☐ Positive ☐ Not evaluated

Carcinoma type *(tick only one)*: ☐ Ductal carcinoma ☐ Lobular carcinoma

Proliferation index (activity by Ki67 or MiB1 immunostaining): _____ % of positive cells

Germ cell tumour risk factors and staging at diagnosis *(Germ cell tumours only)*:

Histological classification: ☐ Seminoma ☐ Non-seminoma

Site of origin: ☐ Gonadal
☐ Extra-gonadal: ☐ retroperitoneal ☐ mediastinal ☐ Other sites; specify: _____

INHERITED DISORDERS
Primary Immune Deficiencies (PID) - *main disease code 8*

DISEASE

Classification:

- ☐ Absence of T and B cells SCID
- ☐ Absence of T, normal B cell SCID
- ☐ ADA deficiency (Adenosine deaminase deficiency)
- ☐ Ataxia telangiectasia
- ☐ Bare lymphocyte syndrome
- ☐ Cartilage hair hypoplasia
- ☐ CD 40 Ligand deficiency
- ☐ Chediak-Higashi syndrome
- ☐ Chronic granulomatous disease
- ☐ Common variable immunodeficiency
- ☐ DiGeorge anomaly
- ☐ Immune deficiencies, not otherwise specified
- ☐ Kostmann syndrome-congenital neutropenia
- ☐ Leukocyte adhesion deficiencies
- ☐ Neutrophil actin deficiency
- ☐ Omenn syndrome
- ☐ PNP deficiency (Purine nucleoside phosphorylase deficiency)
- ☐ Reticular dysgenesis
- ☐ SCID, other; specify: _____
- ☐ SCID, unspecified
- ☐ Wiskott Aldrich syndrome
- ☐ X-linked lymphoproliferative syndrome
- ☐ Other; specify: _____

INHERITED DISORDERS
Inherited Disorders of Metabolism - *main disease code 8*

DISEASE

Classification:

☐ Adrenoleukodystrophy
☐ Aspartyl glucosaminuria
☐ B-glucuronidase deficiency (VII)
☐ Fucosidosis
☐ Gaucher disease
☐ Glucose storage disease
☐ Hunter syndrome (II)
☐ Hurler syndrome (IH)
☐ I-cell disease
☐ Krabbe disease (globoid leukodystrophy)
☐ Lesch-Nyhan (HGPRT deficiency)
☐ Mannosidosis
☐ Maroteaux-Lamy (VI)
☐ Inherited disorders of metabolism, not otherwise specified
☐ Metachromatic leukodystrophy
☐ Morquio (IV)
☐ Mucolipidoses, unspecified
☐ Mucopolysaccharidosis (V)
☐ Mucopolysaccharidosis, unspecified
☐ Niemann-Pick disease (Type A,B)
☐ Niemann-Pick disease (Type C,D,E)
☐ Neuronal ceroid – lipofuscinosis (Batten disease)
☐ Polysaccharide hydrolase abnormalities, unspecified
☐ Sanfilippo (III)
☐ Scheie syndrome (IS)
☐ Wolman disease
☐ Other; specify: _____

INHERITED DISORDERS
Platelet and Other Inherited Disorders - *main disease code 8*

DISEASE

Classification:

☐ Glanzmann thrombasthenia
☐ Other inherited platelet abnormalities: specify: _____
☐ Osteopetrosis (malignant infantile osteopetrosis)
☐ Other osteoclast defects: specify: _____

HISTIOCYTIC DISORDERS
main disease code 9

DISEASE

Classification:

- ☐ Histiocytic disorders, not otherwise specified
- ☐ Familial erythro/haemophagocytic lymphohistiocytosis (FELH)
- ☐ Langerhans Cell Histiocytosis (Histiocytosis-X)
- ☐ Haemophagocytosis (reactive or viral associated)
- ☐ Histiocytic sarcoma (malignant histiocytosis)
- ☐ Other; specify: _____

AUTOIMMUNE DISORDERS
main disease code 10

DISEASE

Classification:

Connective tissue:

☐ Systemic sclerosis (SS)

Involvement/clinical problem:
- ☐ diffuse cutaneous
- ☐ limited cutaneous
- ☐ SSc sine scleroderma
- ☐ Mixed Connective Tissue Disease (MCTD)
- ☐ Other; specify: _____

☐ Systemic lupus erythematosus (SLE)
☐ Polymyositis dermatomyositis
☐ Sjögren syndrome
☐ Antiphospholipid syndrome
☐ Other type of connective tissue disease; specify: _____

Vasculitis:

☐ Wegener granulomatosis
☐ Classical polyarteritis nodosa
☐ Microscopic polyarteritis nodosa
☐ Churg-Strauss
☐ Giant cell arteritis
☐ Takayasu
☐ Behçet syndrome
☐ Overlap necrotising arteritis
☐ Other; specify: _____

Arthritis:

☐ Rheumatoid arthritis
☐ Psoriatic arthritis/psoriasis
☐ Juvenile idiopathic arthritis (JIA), systemic (Still's disease)
☐ Juvenile idiopathic arthritis (JIA), articular
- ☐ oligoarticular onset
- ☐ polyarticular onset

☐ Other Juvenile idiopathic arthritis; specify: _____
☐ Other arthritis; specify: _____

AUTOIMMUNE DISORDERS
main disease code 10

DISEASE continued

Classification:

Neurological diseases:

- ☐ Multiple Sclerosis
- ☐ Myasthenia gravis
- ☐ Amyotrophic lateral sclerosis (ALS)
- ☐ Chronic inflammatory demyelinating polyneuropathy (CIDP)
- ☐ Neuromyelitis Optica (NMO)
- ☐ Other autoimmune neurological disorder; specify: _____

Haematological diseases:

- ☐ Idiopathic thrombocytopenic purpura (ITP)
- ☐ Haemolytic anaemia
- ☐ Evan syndrome
- ☐ Autoimmune lymphoproliferative syndrome (primary diagnosis, not subsequent to transplant)
- ☐ Other haematological autoimmune disease; specify: _____

Bowel diseases:

- ☐ Crohn's disease
- ☐ Ulcerative colitis
- ☐ Other autoimmune bowel disease; specify: _____

Other autoimmune diseases:

- ☐ Grave's disease
- ☐ Insuline-dependent diabetes (IDD)
- ☐ Other autoimmune disease; specify: _____

OTHER PRIMARY DISEASES
Infections - *main disease code 14*

DISEASE

Classification:

☐ Prevention/Prophylaxis

☐ Treatment:

Pathogen involved:

- ☐ Adenovirus
- ☐ BK virus
- ☐ Cytomegalovirus (CMV)
- ☐ Epstein-Barr virus
- ☐ Human herpes virus
- ☐ Human immunodeficiency virus (HIV)
- ☐ Other virus; specify: _____
- ☐ Candida
- ☐ Aspergillus
- ☐ Other fungus; specify: _____
- ☐ Other infection; specify: _____

OTHER PRIMARY DISEASES
Neurological Disorders - *main disease code 12*

DISEASE

Classification:

- ☐ Duchenne muscular dystrophy
- ☐ Acute cerebral vascular ischemia
- ☐ Amyotrophic lateral sclerosis (ALS)
- ☐ Parkinson's disease
- ☐ Spinal cord injury
- ☐ Cerebral palsy
- ☐ Congenital hydrocephalus
- ☐ Other; specify: _____

OTHER PRIMARY DISEASES
Cardiovascular (Heart) Diseases - *main disease code 13*

DISEASE

Classification:

☐ Acute myocardial infaction (AMI)
☐ Chronic coronary artery disease (ischemic, cardiomyopathy)
☐ Heart failure (non-ischemic etiology)
☐ Other cardiovascular disease
☐ Limb ischemia
☐ Thromboangitis obliterans
☐ Other peripheral vascular disease
☐ Other; specify: _____

OTHER PRIMARY DISEASES
Musculoskeletal Disorders - *main disease code 15*

DISEASE

Classification:

☐ Avascular necrosis of femoral head
☐ Osteoarthritis
☐ Osteogenesis imperfecta
☐ Traumatic joint injury
☐ Other; specify: _____

END OF PRE-INFUSION REGISTRATION & DISEASE CLASSIFICATION SHEETS

Change history:

Version	Date	Description
v1.0	9-Feb-2022	First final version

CELLULAR THERAPIES FORM
-- Day 0 --

CENTRE IDENTIFICATION

EBMT Centre Identification Code (CIC): _____

Hospital: _____

Unit: _____

Contact person: _____

Centre in which the treatment is given (CIC): _____

PATIENT DATA

EBMT Unique Identification Code (UIC): _____
(Patient number in EBMT database; complete if patient had a previous treatment and is already registered in the database)

Date of this report: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Hospital Unique Patient Number or code (UPN): _____
(Compulsory; registrations will not be accepted without this item. All treatments (transplants or CAR T-cell) performed in the same patient must be registered with the same patient identification number or code as this belongs to the patient and not to the treatment.)

Other type of patient identification code(s): _____
(Optional; to be used by the centre to register a patient code for internal use as necessary.)

Initials: _____ / _____ *(first name(s) / family name(s))*

Date of birth: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Sex *(at birth)*:

☐ Male

☐ Female

PREVIOUS THERAPIES incl. BRIDGING THERAPIES
(given before transplant/cellular therapy)

Has the information requested in this section been submitted with a previous HSCT/Cellular Therapy registration for this patient?

☐ No (*continue with this section)*

☐ Yes (*proceed to 'Patient Status at Cellular Therapy' on* *page 5*)

Was the patient treated before this cellular therapy procedure?

☐ No (*proceed to 'Patient Status at Cellular Therapy' on* *page 5*)

☐ Yes: Date started: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Copy and repeat the whole 'Previous Therapies' section for each line of treatment. Do not include preparative/lymphodepleting regimen.

Sequential number of this treatment *(counted from diagnosis)*: __________

☐ Unknown

Chemotherapy/Drugs given?

☐ No *(proceed to "Radiotherapy' on* *page 3*)

☐ Yes *(report below)*

☐ Unknown

List all chemotherapy/drugs given during one line of treatment:

Drug/ Regimen:	**Nº of cycles:**	**Date started:** *(YYYY/MM/DD)*	**Date ended:** *(YYYY/MM/DD)*
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _

PREVIOUS THERAPIES GIVEN BEFORE TRANSPLANT/CELLULAR THERAPY (inlcuding bridging therapies) continued

Copy and repeat the whole 'Previous Therapies' section for each line of treatment. Do not include preparative/lymphodepleting regimen.

List all chemotherapy/drugs given during one line of treatment:

Drug/ Regimen:	**Nº of cycles:**	**Date started:** *(YYYY/MM/DD)*	**Date ended:** *(YYYY/MM/DD)*
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	_ _ _ _/ _ _/ _ _

If there were more drugs given during one line of treatment add more copies of this page.

Radiotherapy:

☐ No

☐ Yes: Date started: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Date ended: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

☐ Unknown

Other treatment:

☐ No

☐ Yes; specify: ________________________

☐ Unknown

PREVIOUS THERAPIES GIVEN BEFORE TRANSPLANT/CELLULAR THERAPY (inlcuding bridging therapies) continued

Copy and repeat the whole 'Previous Therapies' section for each line of treatment. Do not include preparative/lymphodepleting regimen.

Response to this line of treatment:
(complete only the section that is relevant to the main diagnosis for which this cellular treatment is given)

Acute Leukaemias:
- ☐ Complete remission (CR); maintained or achieved
- ☐ Relapse/Progression
- ☐ Not evaluable

MDS and MPN:
- ☐ Complete remission (CR); maintained or achieved
- ☐ Relapse/Progression
- ☐ Improvement but no CR
- ☐ Not evaluable

Plasma cell disorders incl. Multiple Myeloma:
- ☐ Stringent complete remission (sCR)
- ☐ Complete remission (CR)
  - Number of this sCR or CR:
    - ☐ 1st
    - ☐ 2nd
    - ☐ 3rd or higher
- ☐ Very good partial remission (VGPR)
- ☐ Partial remission (PR)
  - Number of this VGPR or PR:
    - ☐ 1st
    - ☐ 2nd
    - ☐ 3rd or higher
- ☐ Stable disease *(no change; includes old MR)*
- ☐ Progression
- ☐ Not evaluable

Haemoglobinopathy:
- ☐ No transfusion required *(in Promise select 'Complete remission'.)*
- ☐ Transfusions required *(in Promise select 'Never in CR'.)*

Lymphomas:
- ☐ Complete remission (CR); maintained or achieved
  - ☐ Unconfirmed
  - ☐ Confirmed, by: ☐ CT scan ☐ PET
- ☐ Partial remission (>50%)
- ☐ No response (<50%)
- ☐ Progression
- ☐ Not evaluable

Bone marrow failure syndrome (incl. Aplastic Anaemia)
- ☐ Complete remission (CR)
- ☐ Partial remission (transfusion and growth factor independent)
- ☐ No response
- ☐ Progression
- ☐ Not evaluable
- ☐ Other

Solid tumours:
- ☐ Complete remission (CR)
- ☐ Stable disease
- ☐ Very good partial remission
- ☐ Progressive disease
- ☐ Partial remission (>50)
- ☐ Minor response (>25% and <50%)
- ☐ Not evaluable

Other diagnoses:
- ☐ Cured *(in Promise select 'Complete remission'.)*
- ☐ Improved *(in Promise select 'Partial remission'.)*
- ☐ Worse *(in Promise select 'Progression'.)*
- ☐ No response
- ☐ Not evaluable

PATIENT STATUS AT CELLULAR THERAPY
(All Diagnoses)

Performance score at initiation of treatment *(choose only one)*:

Type of score used:	Score:									
☐ Karnofsky ☐ Lansky	☐ 10	☐ 20	☐ 30	☐ 40	☐ 50	☐ 60	☐ 70	☐ 80	☐ 90	☐ 100
☐ ECOG	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4					

Patient weight at time of cellular therapy: _____ kg

Patient height at time of cellular therapy: _____ cm

B-cell aplasia at time of cellular therapy?

☐ Absent
☐ Present: Percentage of B-cells: _____ %
☐ Not evaluated

DISEASE STATUS AT CELLULAR THERAPY

Status at cellular therapy:
(complete only the section that is relevant to the main diagnosis for which this cellular treatment is given)

Acute Leukaemias:
- ☐ Primary induction failure
- ☐ Complete remission (CR)
- ☐ Relapse

Lymphomas:
- ☐ Never treated
- ☐ Complete remission (CR)
- ☐ Partial remission (PR)
- ☐ Stable disease (no change/no response)
- ☐ Untreated relapse (from a previous CR) or progression from a previous PR
- ☐ Chemorefractory relapse or progression, including primary refractory disease

MDS, MPN and MDS/MPN:
- ☐ Primary refractory
- ☐ Complete remission (CR)
- ☐ Improvement but no CR
- ☐ Relapse
- ☐ Progression
- ☐ Never treated

Plasma cell disorders incl. Multiple Myeloma:
- ☐ Stringent complete remission (sCR)
- ☐ Complete remission (CR)
- ☐ Very good partial remission (VGPR)
- ☐ Partial remission (PR)
- ☐ Relapse
- ☐ Progression
- ☐ Stable disease (no change/no response)
- ☐ Never treated

Chronic Leukaemias:

CML:
- ☐ Chronic phase
- ☐ Accelerated phase
- ☐ Blast crisis

CLL/ PLL:
- ☐ Complete remission (CR)
- ☐ Partial remission (PR)
- ☐ Stable disease (no change/no response)
- ☐ Relapse
- ☐ Progression
- ☐ Never treated

Solid tumours:
- ☐ Adjuvant
- ☐ Never treated
- ☐ Stable disease (no change/no response)
- ☐ Complete remission (CR)
- ☐ First partial response (PR1)
- ☐ Relapse
- ☐ Progression

Other diagnoses:
- ☐ Cured *(select 'Complete remission'.)*
- ☐ Improved *(select 'Partial remission'.)*
- ☐ Worse *(select 'Progression'.)*
- ☐ No response
- ☐ Not evaluable

COMORBIDITY INDEX

Was there any clinically significant co-existing disease or organ impairment as listed below at time of patient assessment prior to the preparative regimen?

☐ No

☐ Yes *(indicate each comorbidity below)*

☐ Unknown

COMORBIDITY:	Definition:			
Solid tumour, previously present	Treated at any time point in the patient's past history, excluding non-melanoma skin cancer Indicate type: _____	☐ No	☐ Yes	☐ Not evaluated
Inflammatory bowel disease	Crohn's disease or ulcerative colitis	☐ No	☐ Yes	☐ Not evaluated
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	☐ No	☐ Yes	☐ Not evaluated
Infection	Requiring continuation of antimicrobial treatment after day 0	☐ No	☐ Yes	☐ Not evaluated
Diabetes	Requiring treatment with insulin or oral hypoglycaemics but not diet alone	☐ No	☐ Yes	☐ Not evaluated
Renal: moderate/severe	Serum creatinine > 2 mg/dL or >177 µmol/L, on dialysis, or prior renal transplantation	☐ No	☐ Yes	☐ Not evaluated
Hepatic: mild	Chronic hepatitis, bilirubin between Upper Limit Normal (ULN) and 1.5 x the ULN, or AST/ALT between ULN and 2.5 × ULN	☐ No	☐ Yes	☐ Not evaluated
Hepatic: moderate/severe	Liver cirrhosis, bilirubin greater than 1.5 × ULN, or AST/ALT greater than 2.5 × ULN	☐ No	☐ Yes	☐ Not evaluated
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	☐ No	☐ Yes	☐ Not evaluated
Cardiac	Coronary artery disease, congestive heart failure, myocardial infarction, EF ≤ 50%, or shortening fraction in children (<28%)	☐ No	☐ Yes	☐ Not evaluated
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	☐ No	☐ Yes	☐ Not evaluated
Heart valve disease	Except mitral valve prolapse	☐ No	☐ Yes	☐ Not evaluated
Pulmonary: moderate	DLco and/or FEV1 66-80% or dyspnoea on slight activity	☐ No	☐ Yes	☐ Not evaluated
Pulmonary: severe	DLco and/or FEV1 ≤ 65% or dyspnoea at rest or requiring oxygen	☐ No	☐ Yes	☐ Not evaluated
Obesity	Patients with a body mass index > 35 kg/m^2	☐ No	☐ Yes	☐ Not evaluated
Peptic ulcer	Requiring treatment	☐ No	☐ Yes	☐ Not evaluated
Psychiatric disturbance	Depression or anxiety requiring psychiatric consultation or treatment	☐ No	☐ Yes	☐ Not evaluated

Were there any additional major clinical abnormalities not listed above and present prior to the preparative regimen?

Specify: _____

CELLULAR THERAPY TREATMENT

Was the cellular product infused during this treatment/procedure?

☐ Yes

☐ No; Reason why the treatment did not take place:
- ☐ Production failure
- ☐ Out-of-specification product refused by physician
- ☐ Disease progresion
- ☐ Patient condition worsened (ineligible for treatment) or patient died
- ☐ Other; specify: _____

Date of the first cell infusion: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*
(if the cellular therapy product was infused)

OR

Date of last assessment: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*
(only applicable if the cellular therapy product was not infused)

CELLULAR THERAPY INFUSION UNIT(S)

Was there more than one cell infusion unit administered during this treatment?

☐ No

☐ Yes: Indicate number of cell infusion units for this treatment: _____

CELLULAR THERAPY INFUSION UNIT(S)
Description

If more than one cell infusion unit please replicate this section for each one of them.

Identification:

Name of manufacturer:

- ☐ Autolus
- ☐ Bluebird Bio
- ☐ Celgene/ Bristol Myer Squibb
- ☐ Celyad
- ☐ GlaxoSmithKline (GSK)
- ☐ Janssen (Johnson & Johnson)
- ☐ Kite Gilead
- ☐ Miltenyi
- ☐ Novartis
- ☐ Orchard
- ☐ Vertex
- ☐ Local hospital or university
- ☐ Other

CELLULAR THERAPY INFUSION UNIT(S)
Description continued

If more than one cell infusion unit please replicate this section for each one of them.

Identification continued:

Name of product *(if applicable)*:

- ☐ Abecma
- ☐ Breyanzi
- ☐ Cilta-cel
- ☐ Eli-cel
- ☐ Kymriah
- ☐ Tecartus
- ☐ Yescarta
- ☐ Other

Unique ID of the product: _____
(If applicable; enter only if the CT product was infused.)

Batch number: _____
(If applicable; enter only if the CT product was infused.)

Identification of the cell infusion unit given by the centre: _____
(If there is only one cell infusion unit enter "1"; enter only if the CT product was infused)

If the CT product was not infused proceed to 'Survival Status' on page 14.

Was the infused cellular product consistent with the specifications?

- ☐ No
- ☐ Yes

Was the cellular therapy product cryopreserved prior to infusion?

- ☐ No
- ☐ Yes

CELLULAR THERAPY INFUSION UNIT(S)
Manipulation

Complete only for non-commercial products. If more than one cell infusion unit please replicate this section for each of them.

Identification of the cell infusion unit (given by the centre)**:** _____

***Ex-vivo* manipulation of the product contained in the cellular therapy infusion unit:**

☐ No (*proceed to 'Therapy and Cell Infusion' on page 11*)
☐ Yes (*continue with 'Manipulation' section below.*)
☐ Unknown

Manipulation:

Processing/Manufacturing facility:

☐ Onsite, by local cell processing facility
☐ Offsite, by a non-commercial facility
☐ Offsite, by a commercial facility

Gene manipulation:

☐ No

☐ Yes: Type *(check all that apply)*:

☐ Gene transfer: Vector: ☐ Retroviral vector
☐ Lentiviral vector
☐ Other vector; specify: _____

Transgene: ☐ CAR; specify all targets: _____
☐ TCR; specify all targets: _____
specify HLA element: _____
☐ Suicide gene; specify: _____
☐ Other: specify: _____

☐ Gene editing: ☐ No
☐ Yes: Manipulated gene: ☐ CCR5
☐ Factor IX
☐ Factor VIII
☐ Other gene; specify: _____

☐ Other: ☐ No
☐ Yes: specify: _____

CELLULAR THERAPY INFUSION UNIT(S)
Manipulation continued

Complete only for non-commercial products. If more than one cell infusion unit please replicate this section for each of them.

Manipulation aims:

Recognition of a specific target/antigen:

☐ No

☐ Yes: Type *(check all that apply)*:

☐ Viral:
- ☐ Adenovirus
- ☐ BK Virus
- ☐ Covid-19 (SARS-CoV-2)
- ☐ Cytomegalovirus (CMV)
- ☐ Epstein-Barr virus
- ☐ Human herpes virus 6
- ☐ Human immunodeficiency virus (HIV)
- ☐ RSV-CTL
- ☐ Other virus; specify: _____

☐ Fungal:
- ☐ Candida
- ☐ Aspergillus
- ☐ Other fungus; specify: _____

☐ Tumour/cancer antigen(s); specify all: _____

☐ Other target; specify: _____

Cell types *(check all that apply)*:

☐ CD3+ lymphocytes
☐ CD4+ lymphocytes
☐ CD8+ lymphocytes
☐ Gamma-Delta cells
☐ Regulatory T-cells
☐ Mesenchymal
☐ Dendritic cells
☐ CD34+
☐ NK cells
☐ Mononuclear cells (DLI)
☐ Other; specify: _____

Expansion:	**Activation:**	**Induced differentiation:**
☐ No	☐ No	☐ No
☐ Yes	☐ Yes	☐ Yes

THERAPY & CELL INFUSION(S)

Chronological number of cellular therapy treatment for this patient: _____
(Please do not include any transplants the patient has had in the past)

Complete this section only if this is the second or a subsequent cellular therapy for this patient and the previous cellular treatments cannot be registered.

If > 1:

Same package/product as for the previous cellular therapy?

☐ No

☐ Yes

Date of last cellular therapy before this one: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Type of last cellular therapy before this one:

☐ Auto

☐ Allo: Was the same donor used for all prior and current cellular therapy? ☐ No ☐ Yes

Was the last cellular therapy performed at another institution?

☐ No

☐ Yes:
CIC (if known): _____
Name of institution: _____
City: _____

If > 1 submit an annual follow-up form before proceeding using the latest assessment date before this cellular therapy; this is so relapse data and other events between transplants/cellular therapies can be captured.

Reason for this cellular therapy (check all that apply)**:**

If indication is the <u>treatment of a primary disease:</u>

☐ Treatment of primary diagnosis
☐ Prevention of disease relapse or progression
☐ Rescue from disease relapse or progression
☐ Minimal residual disease reduction
☐ Refractory disease
☐ Other; specify: _____

If indication is the <u>treatment or prevention of a complication derived from a previous treatment:</u>

GvHD
☐ Unrelated to GvHD
☐ Prevention/Prophylaxis of GvHD
☐ Treatment of GvHD

Graft function
☐ Unrelated to graft function
☐ Preventionof rejection/Promotion of cell engraftment
☐ Graft enhancement
☐ Graft failure treatment

Immune reconstitution
☐ Unrelated to immune reconstitution
☐ Immune reconstitution

THERAPY & CELL INFUSION(S)
Preparative Treatment

Did the patient receive preparative (lymphodepleting) treatment?

☐ No

☐ Yes: Specification and dose of the preparative regimen:

Include any systemic drugs (chemotherapy, growth factors, antibodies, etc.

Name of drug *(any given before day 0)*	**Total prescribed cumulative dose*** *(as per protocol)*	**Units**		
		☐ mg/m²	☐ mg/kg	☐ AUC**
		☐ mg/m²	☐ mg/kg	☐ AUC**
		☐ mg/m²	☐ mg/kg	☐ AUC**
		☐ mg/m²	☐ mg/kg	☐ AUC**
		☐ mg/m²	☐ mg/kg	☐ AUC**
		☐ mg/m²	☐ mg/kg	☐ AUC**

** Report the total prescribed cumulative dose as per protocol. Multiply daily dose in mg/kg or mg/m² by the number of days; eg. for Busulfan given 4mg/kg daily for 4 days, total dose to report is 16mg/kg*

*** AUC: Area under the curve*

Other type of preparative treatment:

☐ No

☐ Yes; specify: _____

CELL INFUSION EPISODE(S)

Was there more than one cell infusion episode during this treatment or procedure?

☐ No

☐ Yes: Number of different cell infusion episodes during this treatment/procedure: _____

CELL INFUSION EPISODE(S)
Description

If more than one cell infusion episode please replicate this section for each of them.

Date of cell infusion episode: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Route of infusion:

☐ Intravenous

☐ Intrathecal

☐ Intratumour injection

☐ Other route; specify: _____

Combined/concomitant therapies planned before this cellular therapy to optimize efficiency?

☐ No

☐ Yes; specify: _____

Treatment given: ☐ Simultaneously to the cellular therapy

☐ After the cellular therapy episode was finished

If more than one unit was used, indicate the identification of the cell infusion given by the centre as described in the 'Cell Infusion Unit' section *(This item is mandatory if more than one cell infusion unit was used.)*: _____

Is the exact number of cells infused available?

☐ No, only a range is available

☐ Yes: Number of cells: _____ *(not adjusted for cell viability)*

Unit *(tick only one)*: ☐ 10^6/kg ☐ 10^6 ☐ 10^8/kg ☐ 10^8

Cell viability: _____ **%**

If more than one unit was used, indicate the identification of the cell infusion given by the centre as described in the 'Cell Infusion Unit' section *(This item is mandatory if more than one cell infusion unit was used.)*: _____

Is the exact number of cells infused available?

☐ No, only a range is available

☐ Yes: Number of cells: _____ *(not adjusted for cell viability)*

Unit *(tick only one)*: ☐ 10^6/kg ☐ 10^6 ☐ 10^8/kg ☐ 10^8

Cell viability: _____ **%**

SURVIVAL STATUS

Survival status:

☐ Alive

☐ Dead: Date of death *(if death happened around time of cellular therapy)*: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Main cause of death:
(check only one main cause)

☐ Relapse or progression/persistent disease
☐ Secondary malignancy
☐ Cellular therapy-related
☐ HSCT-related *(only if patient previously had a transplant)*
☐ Unknown
☐ Other; specify: _____

Contributory causes of death:
(check all that apply)

☐ GvHD
☐ Cytokine release syndrome
☐ Interstitial pneumonitis
☐ Pulmonary toxicity
☐ Infection: ☐ bacterial
☐ viral
☐ fungal
☐ parasitic
☐ unknown
☐ Rejection/Poor graft function
☐ History of severe veno occlusive disorder (VOD)
☐ Haemorrhage
☐ Cardiac toxicity
☐ Central nervous system (CNS) toxicity
☐ Gastrointestinal (GI) toxicity
☐ Skin toxicity
☐ Renal failure
☐ Multiple organ failure
☐ Other; specify: _____

END OF DAY 0 REGISTRATION

Change history:

Version	Date	Description
v1.0	9-Feb-2022	First final version
v2.0	23-May-2022	Typos corrected Disease status at time of CT: label sets for MDS, MPN and MDS/MPN; Solid Tumors and Plasma cell disorders incl. Multiple Myeloma updated

CELLULAR THERAPIES FORM
-- Day 100, 6 Months & Annual Follow-Up --

EBMT Unique Identification Code (UIC): _____
(Patient number in EBMT database)

Date of this report: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

CENTRE IDENTIFICATION

EBMT Centre Identification Code (CIC): _____

Unit: _____

Contact person: _____

PATIENT DATA

Hospital Unique Patient Number or code (UPN): _____
(Compulsory; registrations will not be accepted without this item. All treatments (transplants or CAR T-cell) performed in the same patient must be registered with the same patient identification number or code as this belongs to the patient and not to the treatment.)

Other type of patient identification code(s): _____
(Optional; to be used by the centre to register a patient code for internal use as necessary.)

Initials: _____ / _____ *(first name(s) / family name(s))*

Date of birth: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Sex *(at birth)***:**
☐ Male
☐ Female

Assessment period covered by this report:
☐ Day 100
☐ 6 Months
☐ Annual Follow-Up

RECOVERY

Absolute neutrophil count (ANC) recovery *(Neutrophils ≥ 0.5x10^6 cells/L)*:

☐ No: Date of last assessment: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

☐ Yes: Date of ANC recovery: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*
(first of 3 consecutive values after 7 days without transfusion containing neutrophils)

☐ Never below

☐ Unknown

Platelet reconstitution:

Platelets **≥ 20x10^9 cells/L**:

☐ No: Date of last assessment: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

☐ Yes: Date of platelet reconstitution: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*
(first of 3 consecutive values after 7 days without platelet transfusion)

- ☐ Date unknown; patient discharged before levels reached
- ☐ Date unknown; out-patient

☐ Never below

☐ Unknown

Platelets **≥ 50x10^9 cells/L**:

☐ No: Date of last assessment: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

☐ Yes: Date of platelet reconstitution: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*
(first of 3 consecutive values after 7 days without platelet transfusion)

- ☐ Date unknown; patient discharged before levels reached
- ☐ Date unknown; out-patient

☐ Never below

☐ Unknown

Date of last platelet transfusion: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* ☐ Not applicable *(not transfused)*

RESPONSE TO CELLULAR THERAPY

Complete only for Day 100 and 6 Months.

Best clinical/biological response after the entire cellular therapy treatment:

If the indication was the treatment of a primary disease:

☐ Complete remission (CR) / Normalisation of organ function / No infection present
☐ *for AML only:* Complete remission with incomplete haematological recovery (CRi)
☐ Partial remission / Partial or non-normalisation of organ function
☐ No response
☐ Disease progression or worsening of organ function
☐ Not evaluated

Date response evaluated: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

LAST CONTACT DATE FOR THIS REPORT

Date of last assessment for this report: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*
(enter date of advanced cellular therapy plus the set period - Day 100, 6 Months, Annual Follow-Up - approximately)

CURRENT HAEMATOLOGICAL FINDINGS

Was a haematological investigation performed?

☐ No

☐ Yes:

Hb	_____ g/dl
Platelets	_____ 10^9 cells/L
Were platelets transfused within 7 days before date of test?	☐ No ☐ Yes
White blood cells	_____ 10^9 cells/L
Haematocrit	_____ %
Were RBC transfused within 30 days before date of test?	☐ No ☐ Yes
Percentage Lymphocytes	_____ %
Percentage Neutrophils	_____ %

B-cell aplasia since last assessment:

☐ Absent

☐ Present: Percentage of B-cells: _____ % *(If the patient received tretament for B-cell aplasia, add details in "Post-Therapy Treatment' on page 16)*

☐ Unknown

PERFORMANCE SCORE

Performance score at the last assessment *(choose only one)*:

Type of score used:	Score:
☐ Karnofsky ☐ Lansky	☐ 10 ☐ 20 ☐ 30 ☐ 40 ☐ 50 ☐ 60 ☐ 70 ☐ 80 ☐ 90 ☐ 100
☐ ECOG	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

COMPLICATIONS SINCE THE LAST REPORT
-- GvHD --

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

Did graft versus host disease (GvHD) occur?

☐ No *(proceed to 'Complications since last report - Toxicities (non-infectious)' on page 5)*

☐ Yes: Type of GvHD *(check all that apply)*:

☐ **Acute GvHD:** Maximum grade: ☐ I ☐ II ☐ III ☐ IV ☐ Present but grade unknown ☐ Not evaluated

Type: ☐ New onset ☐ Recurrent ☐ Persistent

Date of onset: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Stage:

Skin:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4
Liver:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4
Lower GI tract:	☐ 0 *(none)*	☐ 1	☐ 2	☐ 3	☐ 4
Upper GI tract:	☐ 0 *(none)*	☐ 1			
Other site affected:	☐ No	☐ Yes			

Related to cell terapy: ☐ No ☐ Yes

Resolved: ☐ No ☐ Yes

Treatment for acute GvHD:
☐ No
☐ Yes: ☐ Corticosteroids ☐ Monoclonal Antibodies (MoAB) ☐ ATG/ALG ☐ Extra-corporeal photopheresis (ECP) ☐ Other; specify: _____

☐ **Chronic GvHD:** Episode: ☐ First episode ☐ Recurrence ☐ Continuous since last reported episode ☐ Yes, but resolved ☐ Yes, but resolved and reccured again

Date of onset: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Maximum extent during this period: ☐ Limited ☐ Extensive ☐ Unknown

Maximum NIH score during this period: ☐ Mild ☐ Moderate ☐ Severe ☐ Not calculated

COMPLICATIONS SINCE THE LAST REPORT
-- Toxicities (non-infectious) --

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

Toxicities/Non-infectious complications:

☐ No *(proceed to "Complications since last report - Infections' on page 10)*

☐ Yes *(report all non-infectious complications below)*

☐ Unknown *(proceed to "Complications since last report - Infections' on page 10)*

Cytokine release syndrome (CRS): ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Maximum grade: _____ Scale/Criteria used to determine CRS grade:
- ☐ ASBMT/ASTCT
- ☐ Penn
- ☐ CTCAE
- ☐ Lee 2014
- ☐ MDACC
- ☐ CARTOX
- ☐ Other; specify: _____
- ☐ Unknown

Treatment given?
- ☐ No
- ☐ Yes *(If patient was treated for CRS add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Neurotoxicity: ☐ **No** ☐ **Yes**

☐ Altered mental status: Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Aphasia: Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

COMPLICATIONS SINCE THE LAST REPORT
-- Toxicities (non-infectious) --

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

Neurotoxicity *continued*:

☐ Hemiparesis or other focal motor deficit: Onset date: _ _ _ _ / _ _ / _ _ (YYYY/MM/DD) Grade: _____

Treatment given? ☐ No ☐ Yes (add details in 'Post-Therapy Treatment' on page 16)

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Seizures: Onset date: _ _ _ _ / _ _ / _ _ (YYYY/MM/DD) Grade: _____

Treatment given? ☐ No ☐ Yes (add details in 'Post-Therapy Treatment' on page 16)

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Tremors: Onset date: _ _ _ _ / _ _ / _ _ (YYYY/MM/DD) Grade: _____

Treatment given? ☐ No ☐ Yes (add details in 'Post-Therapy Treatment' on page 16)

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Visual hallucinations: Onset date: _ _ _ _ / _ _ / _ _ (YYYY/MM/DD) Grade: _____

Treatment given? ☐ No ☐ Yes (add details in 'Post-Therapy Treatment' on page 16)

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Encephalopathy: Onset date: _ _ _ _ / _ _ / _ _ (YYYY/MM/DD) Grade: _____

Treatment given? ☐ No ☐ Yes (add details in 'Post-Therapy Treatment' on page 16)

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Cerebral oedema: Onset date: _ _ _ _ / _ _ / _ _ (YYYY/MM/DD) Grade: _____

Treatment given? ☐ No ☐ Yes (add details in 'Post-Therapy Treatment' on page 16)

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Other; specify: Onset date: _ _ _ _ / _ _ / _ _ (YYYY/MM/DD) Grade: _____

Treatment given? ☐ No ☐ Yes (add details in 'Post-Therapy Treatment' on page 16)

Resolved: ☐ No ☐ Yes ☐ Unknown

COMPLICATIONS SINCE THE LAST REPORT
-- Toxicities (non-infectious) --

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

Grade 3 and 4 organ toxicities as per CTCAE: ☐ **No** ☐ **Yes** *(select and complete all that apply)*

☐ Skin: Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Liver: Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Lung: Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Heart: Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Kidney: Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Gastrointestinal: Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

☐ Other organ; specify: _____ Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

COMPLICATIONS SINCE THE LAST REPORT
-- Toxicities (non-infectious) --

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

Tumor lysis syndrome (TLS): ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Bone marrow aplasia: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Specify: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Hypogammaglobulinemia: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Was hypogammaglobulinemia present before cellular therapy?
☐ No
☐ Yes: Was it worsened by the cellular therapy? ☐ No ☐ Yes

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Insertional mutagenesis: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Exacerbation of existing neurological disorder: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Specify: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Hemorrhagic stroke: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Grade: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

COMPLICATIONS SINCE THE LAST REPORT

-- Toxicities (non-infectious) --

Do not report complications that were resolved <u>before</u> the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

<u>Other toxicity/complication:</u> ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Specify: ________________________

Grade *(if applicable)*: _________

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

<u>Other toxicity/complication:</u> ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Specify: ________________________

Grade *(if applicable)*: _________

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

<u>Other toxicity/complication:</u> ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Specify: ________________________

Grade *(if applicable)*: _________

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

COMPLICATIONS SINCE THE LAST REPORT
-- Infections --

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

Infection-related complications:
(Report only grade 3 and 4 infections as per CTCAE)

☐ No *(proceed to 'Secondary Malignancies' on page 15)*

☐ Yes *(report all infection-related complications below)*

☐ Unknown *(proceed to 'Secondary Malignancies' on page 15)*

Bacteremia: ☐ **No** ☐ **Yes** *(report all episodes below; in case of the same pathogen report episodes occuring after 14 days)*

1) Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

2) Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

3) Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

4) Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

5) Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

If more than 5 episodes copy this page as necessary.

COMPLICATIONS SINCE THE LAST REPORT
-- Infections continued--

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

Invasive fungal disease including candidemia: ☐ **No** ☐ **Yes**

1) Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

2) Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

3) Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in "Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

4) Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

5) Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

If more than 5 episodes copy this page as necessary.

COMPLICATIONS SINCE THE LAST REPORT
-- Infections continued--

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

CNS infection: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Pneumonia ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

C. difficile infection: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Abdominal infection: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Hepatitis: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Retinitis: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

COMPLICATIONS SINCE THE LAST REPORT
-- Infections continued--

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

Cystitis: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Skin infection: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Upper respiratory tract iunfection: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

CMV reactivation: ☐ **No** ☐ **Yes**
(DNA-emia in serum/plasma/blood)

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Highest number of copies: _____ cp/ml Date of highest copy number: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

EBV reactivation: ☐ **No** ☐ **Yes**
(DNA-emia in serum/plasma/blood/PMN)

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Highest number of copies: _____ cp/ml Date of highest copy number: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

COMPLICATIONS SINCE THE LAST REPORT
-- Infections continued--

Do not report complications that were resolved before the cellular therapy; do not report complications that were previously reported as resolved, unless they reoccured.

HHV6 reactivation: ☐ **No** ☐ **Yes**
(DNA-emia in serum/plasma)

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Highest number of copies: _____ cp/ml Date of highest copy number: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Adenovirus reactivation: ☐ **No** ☐ **Yes**
(DNA-emia in serum/plasma)

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Highest number of copies: _____ cp/ml Date of highest copy number: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Other virus reactivation: ☐ **No** ☐ **Yes**
(DNA-emia in serum/plasma)

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Highest number of copies: _____ cp/ml Date of highest copy number: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

Other infectious complication: ☐ **No** ☐ **Yes**

Onset date: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)* Pathogen: _____

Treatment given? ☐ No ☐ Yes *(add details in 'Post-Therapy Treatment' on page 16)*

Resolved: ☐ No ☐ Yes ☐ Unknown

SECONDARY MALIGNANCIES

Did a secondary malignancy or autoimmune disorder occur?

☐ No

☐ Yes: Diagnosis: _____

Date of diagnosis: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Histologic type *(if applicable)*: _____

Location *(if applicable)*: _____

Secondary malignancy material preserved:

☐ No

☐ Yes

POST-THERAPY TREATMENT

Include only systemic treatments; do not include treatment for acute GvHD as this should be reported in the GvHD section.

Did the patient undergo additional treatment during or immediately after the advanced cellular therapy or since the last reported assessment?

☐ No
☐ Yes: Date started: _ _ _ _ / _ _ / _ _ (*YYYY/MM/DD)*
☐ Unknown

List all chemotherapy/drugs given during one line of treatment:

Drug/ Regimen:	**Indication:** *(as specified in 'Complications' section)*	**Date started:** *(YYYY/MM/DD)*	**Treatment ongoing?**	**Date ended:** *(YYYY/MM/DD)*
		_ _ _ _/ _ _/ _ _	☐ No ☐ Yes	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	☐ No ☐ Yes	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	☐ No ☐ Yes	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	☐ No ☐ Yes	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	☐ No ☐ Yes	_ _ _ _/ _ _/ _ _
		_ _ _ _/ _ _/ _ _	☐ No ☐ Yes	_ _ _ _/ _ _/ _ _

Did the patient receive any other type of additional treatment?

☐ No
☐ Yes; specify: ________________________
☐ Unknown

Is the patient receiving any medication not related to cell therapy or its indications?

☐ No
☐ Yes
☐ Unknown

FIRST RELAPSE/PROGRESSION OR SIGNIFICANT WORSENING AFTER ADVANCED CELLULAR THERAPY

Only applicable when indication was the treatment of a primary disease including infections.

First relapse/progression or significant worsening of organ function of the primary disease:
(detected by any method)

☐ No
☐ Yes: Date of relapse: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*
☐ Continuous progression since advanced cellular therapy

LAST DISEASE STATUS

Only applicable when indication was the treatment of a primary disease including infections.

Last disease status:

☐ Complete remission/Normalisation of organ function/No infection present
☐ Partial remission
☐ No response
☐ Disease progression or worsening of organ function
☐ Not evaluated

Histological verification of relapse *(only applicable to lymphoma with status relapse)*:

☐ No
☐ Yes

Transfusion status *(only applicable to haemoglobinopathies)*:

☐ No transfusion required
☐ Transfusion required

Disease burden:

LDH level:

☐ Normal
☐ Elevated
☐ Not evaluated

Inflammatory state (C-reactive protein [CPR] concentration):

☐ Normal
☐ Elevated: Maximum CRP concentration: _____ Unit *(check only one)*: ☐ mg/dL ☐ mg/L
☐ Not evaluated

Date of C-reactive protein level assessment: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

HOSPITAL ADMISSION

Complete only for Day 100 and 6 Months.

Was inpatient admission and care needed?

☐ No
☐ Yes
☐ Unknown

Was the patient transferred to the intensive care unit (ICU)?

☐ No
☐ Yes
☐ Unknown

PREGNANCY AFTER CELLULAR THERAPY

Complete only for 6 Months and Annual Follow-Up.

Has the patient or partner become pregnant after this cellular therapy?

☐ No

☐ Yes: Did the pregnancy result in a live birth?

- ☐ No: Pregnancy outcome: ☐ Abortion (elective, therapeutic, spontaneous)
  ☐ Stillbirth
- ☐ Yes: Newborn status: ☐ Healthy
  ☐ Affected by a disease
  ☐ Information not provided
  Length of term: ☐ Full-term
  ☐ Premature
  ☐ Information not provided
- ☐ Unknown

☐ Unknown

PERSISTENCE OF THE INFUSED CELLS

Were tests performed to assess persistence of the infused cellular products during this period?

☐ No

☐ Yes: Date of the last test: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

Source of cells used for testing: ☐ Bone Marrow
☐ Peripheral blood
☐ Tumour
☐ Other; specify: _____

Technique used for testing: ☐ Molecular (PCR)
☐ Flow cytometry
☐ Chimaerism
☐ Imaging
☐ Immunohistochemistry
☐ Other; specify: _____

Were cells detected: ☐ No
☐ Yes

SURVIVAL STATUS

Survival status:

☐ Alive

☐ Dead: Date of death *(if death happened since last report)*: _ _ _ _ / _ _ / _ _ *(YYYY/MM/DD)*

☐ Lost to follow-up

Main cause of death:
(check only one main cause)

☐ Relapse or progression/persistent disease

☐ Secondary malignancy

☐ Cellular therapy-related

☐ HSCT-related *(only if patient previously had a transplant)*

☐ Unknown

☐ Other; specify: _____

Contributory causes of death:
(check all that apply)

☐ GvHD

☐ Cytokine release syndrome

☐ Interstitial pneumonitis

☐ Pulmonary toxicity

☐ Infection: ☐ bacterial
☐ viral
☐ fungal
☐ parasitic
☐ unknown

☐ Rejection/Poor graft function

☐ History of severe veno occlusive disorder (VOD)

☐ Haemorrhage

☐ Cardiac toxicity

☐ Central nervous system (CNS) toxicity

☐ Gastrointestinal (GI) toxicity

☐ Skin toxicity

☐ Renal failure

☐ Multiple organ failure

☐ Other; specify: _____

END OF FOLLOW-UP REGISTRATION

Change history:

Version	Date	Description
v1.0	9-Feb-2022	First final version

The additional risk minimization measures (aRMMs) for Tecartus are combined with Yescarta and includes the following materials: Healthcare Professional (HCP) Educational Material, Controlled Distribution Program, and Patient Alert Card (PAC). Yescarta and Tecartus are hereafter referred to as Kite cellular therapy products. The key messages of the combined aRMMs for Kite cellular therapy products are presented below.

HCP Educational Material:

Provides a detailed description of how to identify and understand the serious adverse reactions of cytokine release syndrome (CRS) and neurologic adverse reactions associated with the use of either of these two Kite cellular therapy products.

Provides detailed guidance on the treatment and management of CRS and serious neurologic adverse reactions, also known as immune effector cell-associated neurotoxicity syndrome (ICANS).

Asserts that these two Kite cellular therapy products must be administered in a qualified clinical facility and that at least 1 dose of tocilizumab per patient must be available prior to Yescarta or Tecartus infusion, for the treatment of CRS. The clinical facility must have access to an additional dose of tocilizumab within 8 hours of each previous dose.

Instructs that patients must be monitored daily for the first 10 days following infusion of Yescarta or Tecartus for signs and symptoms of CRS, neurologic adverse reactions and other toxicities.

Instructs HCPs to provide patients and/or their caregivers a PAC, to educate the patient about the symptoms of CRS and serious neurologic adverse reactions/ICANS and the need to report the symptoms to their treating doctor immediately. Instructs patients to remain within proximity (within 2 hours of travel), of a qualified clinical facility for at least 4 weeks following infusion.

Specifies that due to the risks associated with these Kite cellular therapy products, infusion should be delayed if a patient has any of the following conditions:

- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions or hypotension) including from preceding chemotherapies
- Active uncontrolled infection or inflammatory disease
- Active graft-versus-host-disease

Specifies that the European Society for Blood and Marrow Transplantation (EBMT) is maintaining a registry for follow up of patients who received Yescarta or Tecartus and additional information can be obtained from: **registryhelpdesk@ebmt.org.** The inclusion of data in the registry does not replace the obligation to spontaneously report adverse events.

Requests HCPs to report any suspected adverse reactions associated with Yescarta or Tecartus to the Marketing Authorisation Holder Kite Pharma EU B.V. or the competent authorities directly and in addition to any recording of data in the Cell Therapy Registry.

Controlled Distribution Program

The EU Summary of Product Characteristics (SmPCs) for Yescarta and Tecartus specify that Yescarta and Tecartus should be administered in a qualified clinical setting to minimize the identified risks associated with administration (e.g., CRS and serious neurologic adverse reactions).

Clinical facilities are required to complete a formal site qualification process prior to ordering Yescarta and/or Tecartus which includes:

- An introduction of HCPs at the clinical facility to Yescarta and/or Tecartus processes (i.e. cell ordering submission, apheresis collection and shipping, final product receipt, handling, onsite training, additional Risk Minimisation Measures).
- A quality audit to ensure the clinical facility meets the required criteria to treat patients with Yescarta and/or Tecartus
- Training of HCPs to include:
  - Standard Operating Procedures on requirements for quality or handling of leukapheresis material and final product
  - Directions for registering a patient, placing a Yescarta and/or Tecartus order and following the cell product journey
  - Additional Risk Minimisation Measures
- A dry run exercise to simulate and practice patient enrolment and cell ordering process
- As part of site qualification training, ensuring HCPs are made aware of the need to contact the Marketing Authorization Holder to obtain recommendations for tumor sample collection and testing following the development of a secondary malignancy.

Patient Alert Card

Provides a warning message for HCPs that the patient has received an engineered autologous T-cell immunotherapy product which can cause severe and even fatal CRS and neurologic adverse reactions.

Provides important reminders for the patients that Kite cellular therapy products can cause serious side effects.

Provides a reminder for the patients to immediately contact their HCP if they experience any of the symptoms listed on the PAC.

Provides date of drug infusion and contact information for the treating HCP.

Provides contact information for the EBMT which is maintaining a registry for follow up of patients who received either of these Kite cellular therapy products.

[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
Eva Vanengelen	QPPV eSigned	02-Jun-2023 15:49:10

Annex 8. List of Significant Changes to the RMP Over Time

Version	Approval date Procedure	Change
1.0	14 December 2020 EMEA/H/C/005102/0000	Not applicable, new submission
1.1	Not applicable EMEA/H/C/005102/II/0008/G	Extension of indication to include adult subjects with Relapsed/Refractory B-ALL. **Part II Safety Specification** Module SI.1: Epidemiology of the indication and target population were updated to include epidemiology data for proposed new indication Module SIII.1: Clinical trial exposure was updated to include safety data from ZUMA-3 Module SVII: Identified and potential risks, and missing information were updated with relevant safety data from ZUMA-3 **Part III Pharmacovigilance Plan** A follow-up questionnaire for New Malignancy was added. **Part VII annexes** Annex 2 was updated to revise protocol link milestones for planned category 1 studies Annex 3 was updated to include clinical trial protocols for ZUMA-3 (KTE-C19-103), and ZUMA-8 (KTE-C19-108) Annex 4: Added new event follow-up questionnaire for New Malignancy
1.2	Not applicable	A recommendation of the Committee for Advanced Therapies to submit a type II variation to amend the conditions of the marketing authorisation to allow suitable alternatives to tocilizumab to be used during periods of tocilizumab shortages listed in the EU shortage catalogue – thereby facilitating continued treatment with Tecartus during such periods. **Part II Safety Specification** Section SVII.3.1.1: The 'Preventability' section of the important identified risk of CRS was updated to align with the changes in the SmPC. **Part V Risk Minimisation Measures** Section V.2: Updated HCP educational material to align with the revised SmPC. **Part VII Annexes** Annex 6: Updated HCP Educational Material.
1.3	16 December 2021 EMEA/H/C/WS2206	Response to the PRAC preliminary assessment report regarding Tocilizumab shortages. **Part II Safety Specification** The 'Preventability' section of the important identified risk of neurologic adverse reaction including cerebral oedema was updated. **Part VII Annexes** Annex 3**:** Updated Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan Annex 6: Updated HCP Educational Material.

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1.4	Under review EMEA/H/C/005102/II/0008/G	Response to requests for supplementary information **Part I: Product Overview** Updated the indication. **Part II: Safety Specification** Module SV: Updated post-marketing data Module SVII.3.1: Updated post-marketing data **Part V: Risk Minimization Measures** Added "Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies." **Part VII: Annex 6** Updated HCP Educational Material. Added "Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies."
2.0	16 December 2021 EMEA/H/C/005102/WS2206/0015	Upversioned following positive CHMP opinion (16 December 2021) regarding tocilizumab shortage.
2.1	Not applicable EMEA/H/C/005102/II/0019	Conditional approval commitment to provide efficacy and safety data of 24 months from study ZUMA-2 **Part II: Safety Specification** Module SI – Editorial changes Module SIII - Updated with current data lock points Module SV: Updated post-marketing data Module SVII: Updated clinical and post-marketing data with data lock points **Part IV: Plan for Post-authorization Efficacy Studies** Removed study ZUMA-2. **Part V: Risk Minimization Measures** Added "Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies." **Part VII:** **Annex 6** Updated HCP Educational Material. Added "Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies."
2.2	Not applicable EMEA/H/C/005102/II/0008/G	Response to requests for supplementary information. **Part I: Product Overview** Updated the indication **Part III: Pharmacovigilance plan** Updated Study KT-EU-472-6036 title. **Part IV: Plan for Post-authorization Efficacy Studies** Updated Study KT-EU-472-6036 title.
2.3	21 July 2022 EMEA/H/C/005102/II/0008/G	**Part I: Product Overview** Updated the indication **Part III: Pharmacovigilance plan** Removed Study KT-EU-472-6036 and ZUMA-3. **Part IV: Plan for Post-authorization Efficacy Studies** Added ZUMA-3 and a specific obligation for ALL.

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3.0	21 July 2022 EMEA/H/C/005102/II/0019 EMEA/H/C/005102/II/0008/G	Consolidation of procedures EMEA/H/C/005102/II/0019 and EMEA/H/C/005102/II/0008/G Annexes Annex 6 was updated with key messages regarding sample collection and testing following the development of a secondary malignancy. Removed of the "Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies."
3.1	Not applicable EMEA/H/C/005102/R/0034	Response to preliminary assessment report requests. **Part IV: Plans for Post-authorization Efficacy Studies** Removed ZUMA-2. Updated milestones for the specific obligations studies for MCL and ALL and added the protocol number and title for the specific obligation for ALL. **Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)** Added 'Controlled distribution program' as an additional risk minimization for secondary malignancy.
3.2	Not applicable EMEA/H/C/WS2632	Aligning the RMP with the SmPC update type II variation to reduce the monitoring time from 10 days to 7 days. **Risk minimization measures** The following plans to evaluate effectiveness were removed: • Collection of evidence for the training delivered to HCPs and other relevant site personnel during site qualification. • A summary of all reported severe, life-threatening CRS and serious neurologic adverse reactions/ICANS with an analysis of adverse event outcomes and treatment. This will be presented within periodic safety reports.
3.3	TBD EMEA/H/C/005102/IB/0044	Update milestone date for KTE-C19-103 specific obligation
3.4 & 4.0	TBD TBD	**Risk minimization measures** The following plan to evaluate effectiveness was reinstated: Collection of evidence for the training delivered to HCPs and other relevant site personnel during site qualification.

[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
[redacted]	Patient Safety eSigned	09-Apr-2024 20:52:40
Rainer Heissing	QPPV eSigned	10-Apr-2024 11:21:57
[redacted]	Regulatory Affairs eSigned	11-Apr-2024 12:23:14