Kite Pharma Inc.

NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY PROTOCOL

Study Title	LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF YESCARTA FOR TREATMENT OF RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA AND PRIMARY MEDIASTINAL B-CELL LYMPHOMA
Protocol ID	KT-EU-471-0117
Protocol Version/Date:	Original: 07 February 2019 Version 1.1: 03 July 2019 Version 1.2: 09 October 2019 Version 1.3: 06 November 2019
EU PAS Register No	(will be entered after EU PAS registration)
Clinical Trials.gov Identifier	Study not registered
Active substance	Axicabtagene ciloleucel
Medicinal Product	YESCARTA®
Product reference	EMEA/H/C/004480
Procedure number	EMEA/H/C/PSP/S/0079
Joint PASS	No
Research Question and Objectives	Primary objective: To evaluate the incidence rate and severity of ADRs in patients treated with YESCARTA, including secondary malignancies, Cytokine Release Syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinemia, and pregnancy outcomes in female patients of childbearing potential. Secondary objectives: To determine the overall survival rate and causes of death after administration of YESCARTA. To determine the time to next treatment after administration of YESCARTA.

	To determine the time to relapse or progression of primary disease after administration of YESCARTA. To assess the safety and effectiveness profile by gender, age, ethnicity, and in special populations (patients with prior allogeneic SCT, high risk comorbidity index, patients treated with Out of Specifications (OOS) product), and additional subgroups may also be explored. To assess the risk of tumor lysis syndrome (TLS) and aggravated Graft Versus Host Disease (GvHD), and the detection of replication competent retrovirus (RCR) in samples of patients with secondary malignancies. Other exploratory objectives: CCI [redacted]
Country (-ies) of study	In countries where YESCARTA will be authorized. At a minimum UK, Spain and Germany will be countries of study, further countries might be added.
Kite Study Director / Author / Contact Person:	Name: PPD Telephone: PPD Email: PPD
Marketing Authorization Holder **MAH contact person**	Kite Pharma EU B.V. Name: PPD Address: Kite Gilead Sciences International Ltd Assoc. Director Regulatory Affairs PPD [redacted] Telephone: PPD Email: PPD
Kite Qualified Person Responsible for Pharmacovigilance:	Name: PPD Telephone: PPD Fax: PPD Email: PPD

CONFIDENTIALITY STATEMENT

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1. TABLE OF CONTENTS

1. TABLE OF CONTENTS 4
LIST OF IN-TEXT TABLES 5
LIST OF IN-TEXT FIGURES 5
2. GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS 6
3. RESPONSIBLE PARTIES 8
4. PROTOCOL SYNOPSIS/ABSTRACT 10
5. AMENDMENTS AND UPDATES 17
6. MILESTONES 18
7. RATIONALE AND BACKGROUND 19
7.1. Rationale for the Current Study 19
8. RESEARCH QUESTIONS AND OBJECTIVES 24
9. RESEARCH METHODS 25
9.1. Study Design 25
9.2. Setting 25
9.2.1. Eligibility 26
9.2.2. Study Centers 26
9.3. Variables 26
9.3.1. Variables utilized for analysis of Primary Objectives 27
9.3.2. Variables utilized for analysis of Secondary Objectives 28
9.3.3. Variables utilized for analysis of Other Exploratory Objectives 29
9.3.4. Variables for exposure to YESCARTA 29
9.3.5. Variables to Collect for Demographics and Baseline Characteristics 29
9.4. Data Sources 30
9.5. Study Size 30
9.6. Data Management 30
9.6.1. Data Transfer Procedure 31
9.7. Data Analysis 31
9.7.1. Primary Endpoints 31
9.7.2. Secondary Endpoints 32
9.7.3. Other Exploratory Endpoints 32
9.7.4. General Considerations for Data Analysis 33
9.7.5. Analysis of Primary Endpoint 34
9.7.6. Analysis of Secondary Endpoints 35
9.7.7. Analysis of Other Exploratory Endpoints 35
9.7.8. Interim Analysis 35
9.8. Quality Control 36
9.9. Limitations of the Research Methods 36
9.10. Other Aspects 37
9.10.1. Study Committee 37
9.10.2. Study Discontinuation 38
10. PROTECTION OF HUMAN SUBJECTS 39
10.1. Good Pharmacoepidemiology and Pharmacovigilance Practices 39
10.2. Informed Consent 39
10.3. Confidentiality 39

11. MANAGEMENT AND REPORTING OF SAFETY INFORMATION 40
11.1. Kite Reporting Requirements to Regulatory Authorities 40
11.2. Definitions 40
11.2.1. Adverse Events 40
11.2.2. Adverse Events of Special Interest 41
11.2.3. Adverse Drug Reactions 41
11.2.4. Serious Adverse Events 41
11.2.5. Serious Adverse Drug Reaction 42
11.2.6. Special Situations Reports 42
12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS 44
12.1. Study Report and Publications 44
12.1.1. Safety Data Reports 44
12.1.2. Annual Reports 44
12.1.3. Final Report 45
12.1.4. Publications, Conference Abstracts, and Manuscripts 45
13. REFERENCES 46
14. APPENDICES 51

Annex 1. List of Stand-Alone Documents 52
Annex 2. ENCePP Checklist for Study Protocols 53
Annex 3. Reference Safety Information 60
Annex 4. Kite Signature Page 98
Annex 5. Cellular and Gene Therapy Form 99

LIST OF IN-TEXT TABLES

Table 1. Table of Responsible Parties 8
Table 2. Protocol Amendments and Updates 17
Table 3. Protocol Milestones 18
Table 4. Selected Signs and Symptoms of CRS and Neurologic Events after CAR T Cells 21
Table 5. Grading of CRS 28

LIST OF IN-TEXT FIGURES

Figure 1. Axicabtagene Ciloleucel Anti-CD19 CAR Construct and Mode of Action 20

2. GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse Event of Special Interest
ALL	Acute lymphoblastic leukemia
ANC	Absolute neutrophil count
aRMMs	additional Risk Minimization Measures
ASCT	Autologous stem cell transplant
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CHMP	Committee for Human Medical Products
CI	Confidence interval
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology of Adverse Events
DLBCL	Diffuse large B-cell lymphoma
EBMT	European Society for Blood and Marrow Transplantation
EMA	European Medicines Agency
EU	European Union
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
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
OOS	Out of specifications
OS	Overall survival
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study

PMBCL	Primary Mediastinal B-cell Lymphoma
PVE	Pharmacovigilance & Epidemiology
QPPV	Qualified Person for Pharmacovigilance
RCR	Replication-competent retrovirus
SAE	Serious adverse event
SADR	Serious adverse drug reaction
scFv	Single-chain variable fragment
SCT	Stem cell transplantation
SSR	Special situation report
TCR	T-cell receptor
US, USA	United States, United States of America

3. RESPONSIBLE PARTIES

Table 1. Table of Responsible Parties

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
Marketing Authorization Holder	PPD Assoc. Director Regulatory Affairs Kite Gilead Sciences International Ltd PPD	Phone: PPD Email: PPD
Study Director	PPD Sr Director, Pharmacovigilance & Epidemiology (PVE)/Epidemiology PPD	Phone: PPD Email: PPD
Medical Monitor	PPD Director, PVE Kite, a Gilead Company PPD	Phone: PPD Email: PPD
Clinical Operations	PPD Senior Clinical Trials Manager Gilead Sciences GmbH PPD	Phone: PPD Fax: PPD Email: PPD
Pharmacovigilance	Pharmacovigilance & Epidemiology Gilead Sciences, Inc. PPD	Phone: PPD Fax: PPD Email: PPD

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
EU QPPV	PPD Vice President, PVE Gilead Sciences GmbH PPD	Phone: PPD Email: PPD Fax: PPD
EBMT Scientific Committee	PPD European Society for Blood and Marrow Transplantation PPD	Phone: PPD Email: PPD Fax: PPD

4. PROTOCOL SYNOPSIS/ABSTRACT

Kite Pharma Inc.

Study Title:	LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF YESCARTA FOR TREATMENT OF RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA AND PRIMARY MEDIASTINAL B-CELL LYMPHOMA
Rationale and Background:	To capture long-term follow-up data for recipients of YESCARTA to evaluate the safety, specifically incidence rates and severity of ADRs including long term safety, the risk of subsequent neoplasm as well as the known and potential risks associated with this product. 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 YESCARTA infusion and for 15 years of follow-up.
Research Question and Objectives:	The primary objective of this study is as follows: • To evaluate the incidence rate and severity of ADRs in patients treated with YESCARTA, including secondary malignancies, Cytokine Release Syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinemia, and pregnancy outcomes in female patients of childbearing potential. The secondary objectives of this study are as follows: • To determine the overall survival rate and causes of death after administration of YESCARTA. • To determine the time to next treatment after administration of YESCARTA. • To determine the time to relapse or progression of primary disease after administration of YESCARTA. • To assess the safety and effectiveness profile by gender, age, ethnicity, and in special populations (patients with prior allogeneic SCT, high risk comorbidity index, patients treated with Out of Specifications (OOS) product), and additional subgroups may also be explored.

- To assess the risk of tumor lysis syndrome (TLS) and aggravated Graft Versus Host Disease (GvHD), and the detection of replication competent retrovirus (RCR) in samples of patients with secondary malignancies.

The other exploratory objectives of this study are as follows:

- CCI [redacted]

Study Design: This is a long-term, non-interventional study of patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL), after two or more lines of therapy, who have been treated with YESCARTA. Patients' data might be entered into the EBMT Registry up to 1 week prior or anytime following YESCARTA infusion and patients will be followed for 15 years in the EBMT registry.

Population: Recipients of YESCARTA for relapsed/refractory diffuse large B-cell lymphomas (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL), after two or more lines of therapy, at participating centers who consent to have data reported to the European Society for Blood and Marrow Transplantation (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, ECOG and Karnofsky score are allowed.

Patients participating in interventional clinical trials 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 Primary Objectives

  Secondary malignancy (date of diagnosis, type, location and relevant details on biopsy/diagnostic results)

  CRS (grade, date of onset, treatment and resolution status)

Neurologic toxicity (type, grade, 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 100 days after the administration of YESCARTA. ANC recovery is defined as neutrophil count $\geq 500/mm^3$ for 3 consecutive days, 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.

Pregnancy that occurs after administration of YESCARTA and additional information related to the outcome of the pregnancy and the newborn's health

- Variables utilized for analysis of Secondary Objectives

  Date and main cause of death, and date of last assessment

  Additional treatment and date of treatment received for primary disease (DLBCL or PMBCL) after YESCARTA administration

  Date of the first relapse or progression or significant worsening of the primary disease (DLBCL or PMBCL) after the YESCARTA infusion

  Grade, date of onset and resolution of TLS

  Type, resolution status, onset date of aggravated GvHD. For acute GvHD: 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

CCI [redacted]

- Variables utilized for analysis of exposure to YESCARTA

  Name and dose level of lymphodepleting chemotherapy received prior to YESCARTA infusion

  YESCARTA infusion: date, and whether YESCARTA was released at physician's request, because the manufactured product was out of specification

- Demographics and Baseline Characteristics

  Age, gender, ethnicity (not collected in the current EBMT Cellular and Gene Therapy Form), and country

  Height and weight at the time of YESCARTA infusion

  Disease subtype (eg, NHL histologies)

  Disease status at time of cellular therapy (eg, sensitive or resistant to chemotherapy or radiation prior to therapy)

  Prior lines of treatment and response

  Disease stage at time of cellular therapy

  Prognostic information: double/triple hit, international prognostic index, cytogenetics (GCB-DLBCL, ABC-DLBCL)

  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

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

Study Size: All eligible patients who have been treated with YESCARTA and documented in the EBMT Registry within five years from study start.

In addition to the further characterisation of the immediate and established toxicities of YESCARTA, the study is designed to detect rare and delayed safety events occurring in patients during 15 person-years of follow up. The available person-years of follow-up are estimated using a piecewise linear survival curve with 50% survival at 2 years and 30% survival long-term. A 10% overall loss to follow-up is assumed. The targeted accrual will provide 95%, or 83%, or 70% likelihood of detecting one event of interest if the true rate is 1 in 100, or 1 in 150, or 1 in 250 over a 15-year period.

Data Analysis:

- **Primary 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
  - 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

- Incidence rates of pregnancy, and pregnancy outcome among women with childbearing potential

- Secondary Endpoints
  - Overall survival
  - Time to next treatment of the primary disease
  - Time to relapse or progression of the primary disease
  - Primary and secondary endpoints on subgroups by gender, age, ethnicity, and in special populations (patients with prior allogeneic SCT, high risk comorbidity index, patients treated with Out of Specifications (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

Analysis of all endpoints for this study will include all patients satisfying the eligibility criteria who are documented within the EBMT Registry and treated with YESCARTA.

Categorical variables will be summarized descriptively by number and percentage of patients in each categorical definition including 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 follow-up period, specified subgroups and other potential confounders (demographics and baseline characteristics, see Section 9.3.5).

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 and time to next treatment, 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 subgroups and other potential confounders (demographics and baseline characteristics; see Section 9.3.5).

Milestones:

Start of data collection:	15 February 2020
End of data collection:	14 November 2039
Study duration:	20 years
Annual Reports:	annually for 5 years, then bi-annually
Final Study report:	14 November 2040

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.

5. AMENDMENTS AND UPDATES

Table 2. Protocol Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1.1	03 July 2019	various	Update	To address the comments of the PRAC Request for a Revised PASS protocol in the PRAC PASS protocol assessment report and to implement the respective changes
1.2	09 October 2019	various	Update	To address the comments of the 2nd PRAC Request for a Revised PASS protocol in the PRAC PASS protocol assessment report and to implement the respective changes
1.3	06 November 2019	various	Update	To address comments of the 3rd PRAC Request for revisions of the PASS protocol 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, the Study Committee and EBMT prior to implementation.

6. MILESTONES

Table 3. Protocol Milestones

Milestone	Planned Date
PRAC approval of study protocol	31 October 2019
Protocol registration in the EU PAS Registry	2 weeks after PRAC approval (15 November 2019)
Start of data collection*	15 February 2020
End of data collection**	14 November 2039
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 - when it will be submitted stand-alone in between PSUR cycles. 2020 to 2024, frequency thereafter to be re-evaluated
Annual reports	Q4 2020 to 2024 annually, then bi-annually at 2026, 2028, 2030, 2032, 2034, 2036, and 2038
Final report of study results	14 November 2040

***** 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 471 0117 will take place three months after protocol registration.
****** 15 years after reaching the defined patient number no further data will be included in the study analyses.

7. RATIONALE AND BACKGROUND

7.1. Rationale for the Current Study

T-cell immunotherapy offers a promising approach for cancer treatment through harnessing the patient's own immune system to destroy malignant cells {June 2015}. Studies with tumor vaccines {Avigan 2008, Kantoff 2010, Nahas 2016, Rosenblatt 2011}, immune checkpoint inhibitors {Hamid 2013, Page 2013}, and tumor-infiltrating lymphocytes {Rosenberg 2011} have demonstrated the potential of T cells to treat cancer. This concept was further proven by the bispecific CD19-directed CD3 T-cell engager (blinatumomab) in B-precursor cell acute lymphoblastic leukemia (ALL) {Topp 2015a, Topp 2015b}.

Chimeric antigen receptors (CARs) are fusion proteins with antigen binding, transmembrane, and T-cell activation domains that, when expressed in T cells, can target tumor antigens for T-cell mediated killing. CAR T cells directed against B-cell antigens have demonstrated promising antitumor activity across B-cell malignancies, including B-cell non-Hodgkin lymphoma (NHL) {Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017, Turtle 2016}, B-cell precursor ALL {Davila 2013, Grupp 2013, Lee 2015, Maude 2014, Maude 2015, Singh 2016}, and chronic lymphocytic leukemia {Kalos 2011, Kochenderfer 2015, Porter 2011}. Engineering T cells with a CAR involves using a replication-incompetent retroviral vector containing the CAR transgene to transduce T cells. Such vectors have been utilized for more than a decade in the design of diverse engineered T-cell products, and the clinical safety profile of these products has shown no evidence of genotoxic events {Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017, Robbins 2015}.

Axicabtagene ciloleucel is an autologous CAR T-cell therapy that targets the pan B-cell marker CD19 that is expressed throughout normal B-cell development and in most B-cell malignancies. The structure of the anti-CD19 CAR construct used for production of axicabtagene ciloleucel and the product's mechanism of action is shown in Figure 1. Briefly, the construct comprises the following domains: an anti-human CD19 single-chain variable fragment (scFv) region; CCI [redacted] human CD28; and the cytoplasmic portion, including the signaling domain, of human CD3ζ, a component of the T-cell receptor complex {Kochenderfer 2009}. The CD28 intracellular signaling domain provides a co-stimulatory signal that works in concert with the primary CD3ζ signal to augment T-cell function, including interleukin (IL)-2 production {Finney 1998}. T cells are CCI [redacted] transduced with the anti-CD19 CAR transgene-containing γ-retroviral vector. The transduced T cells are expanded for several days CCI [redacted], washed, and cryopreserved to generate the YESCARTA T-cell product.

After infusion into the patient, engagement of anti-CD19 CAR T cells with $CD19^+$ target cells triggers CD28 and CD3ζ co-stimulatory domains of the CAR to activate the downstream signaling cascades that lead to activation, proliferation, cytokine production, and acquisition of effector functions, such as cytotoxicity. These signals act in concert and result in proliferation of the CAR T cells and direct killing of target cells. In addition, activated T cells secrete cytokines

and other molecules that can recruit and activate additional anti-tumor immune cells {Restifo 2012}.

Figure 1. Axicabtagene Ciloleucel Anti-CD19 CAR Construct and Mode of Action

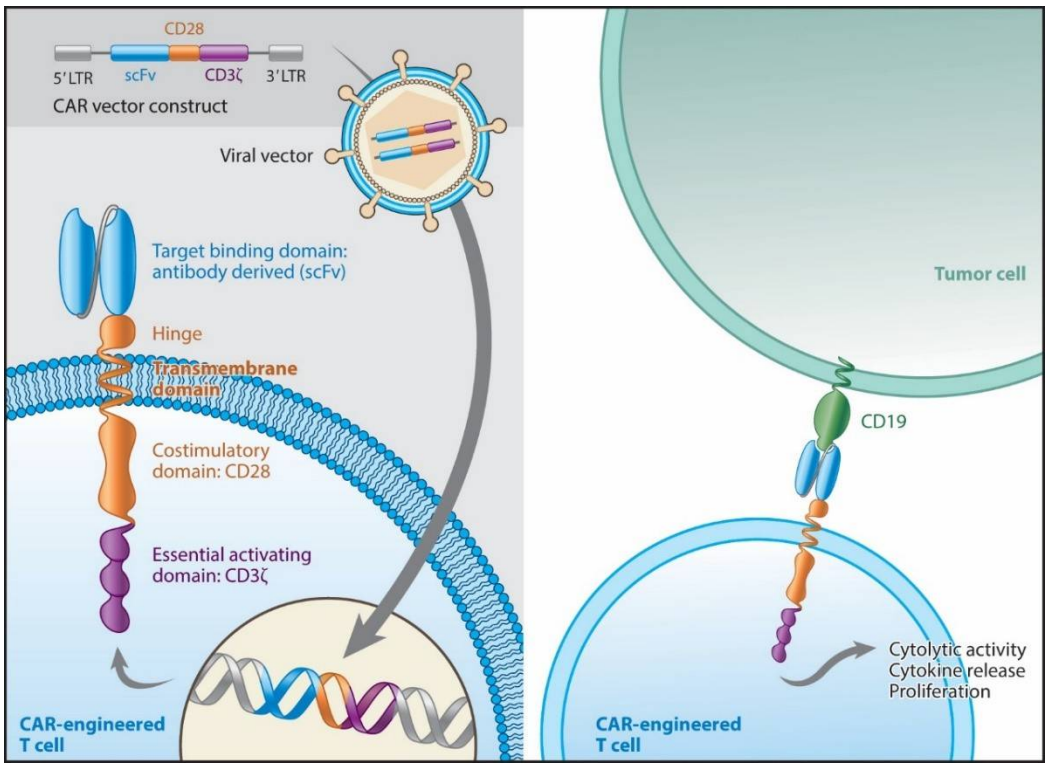

Figure 1: Left panel demonstrates axicabtagene ciloleucel construct with scFv/CD28/CD3ζ, which is inserted in a replication incompetent gamma retroviral vector and, upon transfection of T cells, expresses the chimeric transmembrane protein. The right panel demonstrates the anti CD19 CAR T cell binding to its target CD19 on the tumor cell surface.

Treatment of relapsed or refractory large B-cell lymphomas with anti-CD19 CAR T cells results in a high response rate with durable remissions. In the primary analysis based on the modified intent-to-treat (mITT) population (minimum follow up of 6 months) in the pivotal multicenter trial (ZUMA-1) by Kite Pharma, Inc. (hereafter referred to as Kite), the ORR was 72% and complete response (CR) rate was 51%, as determined by an independent review committee. 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 Cytokine Release Syndrome (CRS) and generally occur within the first week from treatment (Table 4). A revised grading system was proposed by Lee, et al based on the number of affected organs, severity, and therapeutic approaches needed, ie, vasopressors or ventilatory support {Lee 2014}. Secondly, neurologic events are also observed, which can occur either in the presence or absence of CRS with symptoms ranging from fine tremors, aphasia to seizures (Table 4) {Brudno 2016, Lee 2014, Park 2016}. In the ZUMA-1 pivotal trial, the overall rates of CRS and neurologic events were 93% and 64%, respectively. The rates of Grade 3 or higher CRS and

neurologic events were 12% and 31%, respectively. The rate of Grade 5 CRS was 1% (2 subjects). While no Grade 5 neurologic events were reported in the pivotal cohort, Grade 5 events of intracranial hemorrhage (not related to axicabtagene ciloleucel) and cerebral edema (related to axicabtagene ciloleucel) have been reported in the non-pivotal cohorts of ZUMA-1. The median time to onset of first CRS symptoms was 2 days (range: 1 to 12 days) after infusion of axicabtagene ciloleucel. Among the subjects whose CRS symptoms resolved, the median duration of CRS symptoms was 7 days (range: 2 to 29 days, excluding 1 outlying subject with a duration of 58 days). The median time to onset of first neurologic events was 5 days (range: 1 to 17 days). Among the subjects whose neurologic events resolved, the median duration of neurologic events was 13 days (range: 1 to 191 days, excluding 1 outlying subject with a duration of 451 days).

Table 4. Selected Signs and Symptoms of CRS and Neurologic Events after CAR T Cells

Cytokine Release Syndrome	Neurologic Symptoms
Fever	Seizures
Fatigue	Somnolence
Cardiac failure	Headache
Tachycardia	Confusion
Other cardia arrhythmias	Agitation
Dyspnea	Speech impairment
Hypoxia	Tremor
Capillary leak syndrome	Encephalopathy
Chills	Ataxia
Renal function impairment	Memory impairment
Headache	Mental status changes
Malaise	Hallucinations
Liver function abnormalities	Depressed level of consciousness
Nausea	Delirium
Diarrhea	Dysmetria
Hypotension	
Coagulation impairment	

Target-specific toxicities are related to direct cytotoxicity against the tumor and normal B cells expressing the antigens. CD19-specific CAR T cells have a direct effect on B cells, which leads to B-cell aplasia and, consequently, hypogammaglobulinemia {Frey 2016, Grupp 2013, Lee 2015, Maude 2014, Maus 2016}.

Patients with lymphoproliferative disorders, such as B-cell lymphomas, have a higher risk of developing other cancers (subsequent neoplasms) compared to the general population (standardized incidence ratio of 1.25 to 1.43) {Bilmon 2014, Chien 2015, Rossi 2015}. This higher risk results primarily from exposure to prior chemotherapy and radiation either as initial or subsequent treatment or as part of an autologous stem cell transplant (ASCT). The probability of developing a secondary malignancy 10 years after ASCT in patients with lymphoma ranges from 7.9% to 12.9% {Metayer 2003, Seshadri 2009, Smeland 2016}. The types of subsequent neoplasms most commonly observed are acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and melanoma {Bilmon 2014, Metayer 2003, Vaxman 2015}.

Axicabtagene ciloleucel manufacturing relies on a replication defective 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 defective γ-retroviruses encoding a therapeutic T-cell receptor (TCR) or CAR. These findings represent data from 86 unique patients with hematologic malignancies or solid tumors who have follow-up ranging from 3 months to 70 months (5.8 years) {Brentjens 2013, Kochenderfer 2016, Kochenderfer 2012, Kochenderfer 2015, Robbins 2015}. One of these studies (NCI study) is ongoing and - as of December 2018 - has shown no evidence of subsequent neoplasms over a period of up to 23 months in a total of 43 patients with advanced B-cell malignancies treated with retrovirally transduced T cells expressing the same CAR as utilized in axicabtagene ciloleucel {Kochenderfer 2016, Kochenderfer 2012, Kochenderfer 2015}. Long term results from 3 studies to evaluate gammaretroviral vector engineered T-cells for the treatment of HIV showed no treatment-related malignancies 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 samples tested for at least 11 years post-infusion. This analysis represented over 540 patient-years and showed no clinical evidence of viral vector integration-mediated toxicity.

In addition, a retrospective analysis of subjects treated with replication defective γ-retrovirus-transduced T cells across 29 clinical trials spanning from 2001 to 2009, covering 297 individual products and 629 follow-up samples ranging from 1 month to 8 years after infusion, showed no measurable RCR {Bear 2012}. In summary, more than a decade of follow-up of patients treated with T cells engineered to express a TCR or CAR encoded by a γ-retroviral vector has not revealed any cases of genotoxicity that have translated to a subsequent neoplasm.

A theoretical risk remains, however, that genetic modification of T cells with γ-retroviral vectors could result in subsequent neoplasms manifested through insertional mutagenesis introduced during the manufacturing process or by the development of RCR. Although the manufacturing of CAR T cells using vectors similar to the one used in the manufacture of axicabtagene ciloleucel includes provisions to ensure that the virus is replication-incompetent and the likelihood of insertional mutagenesis in differentiated T cells is low, there is a potential risk of insertional mutagenesis and emergence of RCR after these cell products are more broadly used. Exploring the presence of γ-retroviral vector sequences and RCR in the development of subsequent neoplasms is an important step to understand the long-term safety profile of this product.

It should also be noted that axicabtagene ciloleucel is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL), after two or more lines of systemic therapy. The current standard of care for first-line treatment for aggressive B-cell lymphoma is a combination chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine, and prednisolone in combination with an anti-CD20 mAb rituximab (rituximab cyclophosphamide doxorubicin vincristine prednisolone [R-CHOP]). Patients with relapsed or refractory aggressive B-cell lymphoma are typically treated with rituximab and platinum-based combination chemotherapy regimens followed by high-dose chemotherapy followed by autologous hematopoietic stem cell transplant (HDT-ASCT). As such, the risk of subsequent neoplasms due to prior chemotherapy exposure is higher than age-matched healthy controls {Smeland 2015}. Cumulative incidence of subsequent neoplasm 10 years after HDT-ASCT ranges from 5% to 21% {Bilmon 2014, El-Najjar 2014, Forrest 2005, Pirani 2011, Seshadri 2009, Tarella 2011}.

In summary, aggressive large B-cell lymphoma afflicts people over the age of 50 years and predominantly those in the age range between 60 to 65 years of age {Chiu 2015}. The incidence of most malignancies, including hematological malignancies, such as leukemias, and solid tumors, e.g. breast, colorectal, and prostate cancer, increases with age {Howlader 2017}.

The purpose of this study is to analyze and report on the long-term follow-up data for recipients of axicabtagene ciloleucel captured in the EBMT Registry to address the long-term safety of this product, including secondary malignancies, CRS, neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinemia, and pregnancy outcomes in female patients of childbearing potential. The purpose of the study therefore includes the further characterisation of the immediate and recognised toxicities of YESCARTA, as well as the long-term and delayed onset ADRs.

The EBMT is a non-profit organisation that was established in 1974 to allow scientists and physicians involved in clinical bone marrow transplantation to share their experiences and develop co-operative studies. More recently, the scope of the organisation 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 stem cell transplant registry to systematically capture data on all cell therapies. This study will use the data accrued on YESCARTA in the EBMT Registry to systematically evaluate information on patients receiving YESCARTA and for 15 years of follow-up.

8. RESEARCH QUESTIONS AND OBJECTIVES

This is a long-term safety study of recipients of YESCARTA for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

The study will utilize long-term follow-up data for recipients of YESCARTA to evaluate the safety including long term safety, specifically incidence rates and severity of ADRs, the risk of subsequent neoplasm, known and potential risks associated with this product, as well as rare and delayed safety events occurring in patients.

Therefore, the study will make secondary use of the data captured in the EBMT Registry, using the infrastructure EBMT created for the stem cell transplant registry, to systematically capture information at the time of YESCARTA infusion and for 15 years of follow-up.

The primary objective of this study is:

To evaluate the incidence rate and severity of ADRs in patients treated with YESCARTA, including secondary malignancies, Cytokine Release Syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinemia, and pregnancy outcomes in female patients of childbearing potential.

The secondary objectives of this study are:

- To determine the overall survival rate and causes of death after administration of YESCARTA.
- To determine the time to next treatment after administration of YESCARTA.
- To determine the time to relapse or progression of primary disease after administration of YESCARTA.
- To assess the safety and effectiveness profile by gender, age, ethnicity, and in special populations (patients with prior allogeneic SCT, high risk comorbidity index, patients treated with Out of Specifications (OOS) product), and additional subgroups may also be explored. .
- To assess the risk of tumor lysis syndrome (TLS) and aggravated GvHD), and the detection of RCR in samples of patients with secondary malignancies.

The other exploratory objectives of this study are as follows:

- CCI [redacted]

9. RESEARCH METHODS

9.1. Study Design

This study is a long-term, non-interventional study planned to evaluate outcomes of recipients of YESCARTA for treatment of relapsed or refractory DLBCL and PMBCL, after two or more lines of systemic therapy 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. 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 YESCARTA infusion and patients will be followed for 15 years. 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.

9.2. 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 in 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 9.6), 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 (currently dated 15/08/2018)).

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 in their registry 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 its content can 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.

9.2.1. Eligibility

The EBMT Registry collects data on all patients receiving cell therapy. Eligible patient data for this study is from patients treated with YESCARTA for relapsed/refractory diffuse large B-cell lymphomas (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL), after two or more lines of therapy, irrespective of whether the YESCARTA 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 will not be included in the study analyses.

9.2.2. Study Centers

All centers that are qualified for the use of YESCARTA 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 9.2). The centers will enter initial patient data and any subsequent follow up data.

Kite will not interact with the contributing EBMT centers as the relationship is between centers and the EBMT and respective data entry and quality assurance activities are solely handled by the EBMT.

In a commercial setting, Kite is engaging with sites at time of initial commercial center qualification process to allow the prescribing of YESCARTA 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 both initial as well as refresher training to qualified prescriber sites, the contact with centers that are contributing to the EBMT Registry can deliver relevant reminders on the importance of spontaneous reporting and that this is not replaceable by reporting into the EBMT Registry.

9.3. 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 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.

9.3.1. Variables utilized for analysis of Primary Objectives

- Secondary malignancy is defined as the development of any new malignancies, with the exception of relapsed large B-cell lymphomas, occurring after the administration of YESCARTA. The EBMT Registry will collect the date of diagnosis, type, location and, if a biopsy occurred, information whether secondary malignancy was derived from cells that composed or were part of the infused medicinal product or cell/gene therapy product, and this study will utilize this data for analysis.

- 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. The EBMT Registry will collect CRS grade, system of grading, date of onset, treatment and resolution status and this study will utilize this data for analysis.

- Neurologic toxicity is a class effect of CAR T-cell therapies and most commonly includes confusion, delirium, aphasia, obtundation, myoclonus, and seizures. The EBMT Registry will collect the type, grade (according to the Common Terminology of Adverse Events (CTCAE)), treatment, date of onset and resolution status of all neurologic toxicities, and this study will utilize this data for analysis.

- Prolonged cytopenias are defined as inability to recover the absolute neutrophil count (ANC) and platelets within 100 days after the administration of YESCARTA. ANC recovery is defined as neutrophil count $\geq 500/mm^3$ for 3 consecutive days, and platelet recovery is defined as platelet count $\geq 50 \times 10^9/L$ without transfusion support within 7 days. The EBMT Registry will collect the date of recovery for ANC and platelets, and this study will utilize this data for analysis.

- 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 EBMT Registry will collect the type, organism, treatment and date of onset of infection as well as resolution, and this study will utilize this data for analysis.

- Hypogammaglobulinemia is defined as serum IgG levels below 600 mg/dL. The EBMT Registry will collect for hypogammaglobulinemia the date of onset, treatment, and resolution status, and this study will utilize this data for analysis.

- The EBMT Registry will collect data on any pregnancy that occurs after administration of YESCARTA and additional information related to the outcome of the pregnancy and the newborn's health, and this study will utilize this data for analysis.

Table 5. 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).

9.3.2. Variables utilized for analysis of Secondary Objectives

- Date and main cause of death, and date of last assessment
- Additional treatment and date of treatment received for primary disease (DLBCL or PMBCL) after YESCARTA administration
- Date of the first relapse or progression or significant worsening of the primary disease (DLBCL or PMBCL) after the YESCARTA infusion
- Grade, date of onset and resolution of Tumor lysis syndrome (TLS)
- Type, resolution status, onset date of GvHD. For acute GvHD: grade, and relationship to YESCARTA
- 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)

9.3.3. Variables utilized for analysis of Other Exploratory Objectives

CCI

9.3.4. Variables for exposure to YESCARTA

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

9.3.5. Variables to Collect for Demographics and Baseline Characteristics

- Age, gender, ethnicity (not collected in the current EBMT Cellular and Gene Therapy Form) and country
- Height and weight at the time of YESCARTA infusion
- Disease subtype (eg, NHL histologies)
- Disease status at time of cellular therapy (eg, sensitive or resistant to chemotherapy or radiation prior to therapy)
- Prior lines of treatment and response
- Disease stage at time of cellular therapy
- Prognostic information: double/triple hit, international prognostic index, cytogenetics (GCB-DLBCL, ABC-DLBCL)
- 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

9.4. 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 YESCARTA 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 MED- A and/or 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.

9.5. Study Size

This study plans to evaluate all eligible patients who have been treated with YESCARTA and documented in the EBMT Registry within five years from study start, and to follow these patients for 15 years. In addition to the further characterisation of the immediate toxicities of YESCARTA, the study is designed to detect rare safety events occurring in patients. Therefore, the primary analysis will consist of estimation of the rate of endpoint events per 15 person-years of follow up and the cumulative incidence of the event by 15 years, along with 95% confidence intervals (CIs). The events of interest (i.e., those described in Section 9.3.1) are subject to competing risks of death, which decrease the available person-years of follow-up. The available person-years of follow-up are estimated using a piecewise linear survival curve with 50% survival at 2 years and 30% survival long-term, indicating an average person-years of follow-up of 6.7 years. A 10% overall loss to follow-up is further assumed, resulting in total person-years of follow-up of approximately 4522. This number of person-years of follow-up will provide 95%, or 83%, or 70% likelihood of seeing at least one event of interest, if the true rate per 15 years of follow up is at least 1:100, or 1:150, or 1:250 respectively.

9.6. 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 have access to the EBMT Registry database. EBMT will cooperate with centers to reduce the amount of missing/erroneous data in the registry. Kite will not interact with the centers.

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 Day 100, 6 and 12 months and then annually for 15 years after infusion. 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 time lines as described in section 11.

The center that administers YESCARTA 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 YESCARTA 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 12.1.

9.6.1. Data Transfer Procedure

EBMT provides raw data outputs in a standard format to Kite. Safety datasets are provided quarterly and full datasets annually.

9.7. Data Analysis

9.7.1. Primary 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
- 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

- Incidence rates of pregnancy, and pregnancy outcome among women with childbearing potential

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 YESCARTA 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 YESCARTA infusion + 1. Deaths before experiencing the event will be taken as a competing risk.

9.7.2. Secondary Endpoints

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

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

- Time to relapse or progression of the primary disease: time to relapse or progression is defined as the time from YESCARTA infusion to the first relapse or progression or significant worsening of the primary disease (DLBCL or PMBCL), 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.

- Primary and secondary endpoints on subgroups by gender, age, ethnicity, and in special populations (patients with prior allogeneic SCT, high risk comorbidity index, patients treated with Out of Specifications (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.

9.7.3. Other Exploratory Endpoints

- CCI [redacted]

- CCI [redacted]

9.7.4. 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 satisfying the eligibility criteria who are documented within the EBMT Registry and treated with YESCARTA. Categorical variables will be summarized descriptively by number and percentage of patients in each categorical definition including 95% confidence intervals (CIs). Continuous variables will be summarized descriptively by mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum.

Incidence rates of endpoint events will be provided, except where indicated. Multivariate Poisson regression analyses will be used to estimate incidence rates, adjusted for follow-up period, specified subgroups and other potential confounders (demographics and baseline characteristics; see Section 9.3.5).

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 and time to next treatment, 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 subgroups and other potential confounders (demographics and baseline characteristics; see Section 9.3.5).

The analysis will be firstly based on complete case analysis when the percentage of missing is around 5-10%. However, the potential impact of the missing values on the analysis will be also 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 describe above and in Section 9.7.5 and 9.7.6. 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 as sensitivity analyses 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).

9.7.5. Analysis of Primary Endpoint

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 YESCARTA 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 YESCARTA infusion. Treatment and resolution of neurologic toxicities will be described.

Prolonged cytopenias: The proportion of patients who fail to recover neutrophil and platelet counts, as previously specified, by Day 100 after the administration of YESCARTA will be described along with 95% CI using exact binomial methods.

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 YESCARTA 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 YESCARTA 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 therapy will also be described as part of this endpoint.

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.

9.7.6. Analysis of Secondary Endpoints

Overall survival: Overall survival (OS) is the time from date of YESCARTA 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.

Time to next treatment: 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 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.

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 YESCARTA 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 YESCARTA infusion and 95% CI will be estimated using competing risk analysis. The severity and relationship to YESCARTA will also be summarized.

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

9.7.7. Analysis of Other Exploratory Endpoints

CCI [redacted]

[redacted]

9.7.8. Interim Analysis

Annual reports will be prepared for the first five years and then bi-annually, in which an analysis of treated patients for the primary and secondary endpoints will be included. The study objective is 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 YESCARTA.

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 YESCARTA within 30 days (45 days for the first report). Two quarterly reports will be submitted as appendices to the PSUR to the PRAC. In case an intervening quarterly report identifies a major new safety finding, the respective report will be submitted promptly as stand-alone document.

9.8. 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 are done, including the analyses of outliers, additional data requests and if needed statistic adjustments for missing data.

Apart from remote monitoring activities, on-site monitoring of data for 10% of the included YESCARTA 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 or 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 was not submitted for a patient during the 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 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 study monitoring plan.

9.9. Limitations of the Research Methods

This study is a non-comparative non-interventional study, as a result confounding by indication should be a minimal issue in the absence of a comparator. Multivariate analyses will aim to

minimize potential confounding by indication by including disease assessment and according treatment in the analyses.

The EBMT Registry allows patient data entry any time after YESCARTA infusion; therefore this study has the characteristic disadvantages of retrospective studies, for example, 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.

Information bias can be prevented by using standard measurement instruments, like 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.

9.10. Other Aspects

9.10.1. Study Committee

A Study Committee will be established to monitor this study. Membership will be comprised of representatives from Kite and representatives from the EBMT team. Additional investigators with expertise on CAR T cells and late effects after transplantation may be invited as necessary and as determined by the Study Committee.

9.10.1.1. Responsibilities

The Study Committee regularly reviews the study progress and its analysis results and provides input from the point of view of the organization/committee that it represents. The Study Committee can consider publication and other analysis in the data that is also used for this study and limits the actual study analyses and reviews to sponsor and EBMT. Some of the specific responsibilities of the Study Committee include:

- Review the study protocol and statistical analysis plan and approve updates and amendments, as necessary
- Review and approve the overall study structure
- Provide scientific guidance
- Review results of predefined annual and final analyses, as well as adhoc analyses
- Review prepared reports

Any individual adverse drug reactions that are observed and assessed by participating investigators to be associated with any Kite products will be reported through the standard post-market spontaneous pharmacovigilance reporting process following the standard time lines. The investigators or designated clinicians will report adverse drug reactions directly to Kite in accordance with applicable laws and regulations as described in section 11.

9.10.2. Study Discontinuation

No patient's treatment will be dictated by the protocol of this long-term observational study or by the Study Committee, EBMT, or Kite. Consequently, continuing or discontinuing this study will not impact patient care. Therefore, identification of adverse effects of YESCARTA 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 reduces to unacceptable levels because of low exposure rates, extremely slow patient accrual, or loss of the ability to follow-up

In the event that such conditions are met, any consideration for termination of the study will be discussed and agreed with the European Medicines Agency (EMA) beforehand.

10. 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 YESCARTA.

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, 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 will be benefiting future patients. The only risk to patients is the risk of loss of privacy and confidentiality. This is a well-mitigated risk in relationship to the potential benefit to future recipients from knowledge gained through these research studies.

10.1. Good Pharmacoepidemiology and Pharmacovigilance Practices

The study will be conducted in accordance with the European Medicines Agency Guideline on Good Pharmacovigilance Practices (GVP) Modules VI and VIII Post-Authorisation Safety Studies, 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.

10.2. Informed Consent

No specific informed consent will be obtained to participate in this secondary analysis of existing data. 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 be consenting to provide their data into the EBMT Registry.

10.3. 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.

11. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

The operational model for this post-authorization safety study protocol qualifies as non-interventional research with a design based on secondary use of data (i.e. utilizing data from patients 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. By 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 time lines. The centers will report any suspected adverse reactions directly to Kite, health authorities or to the EMA. The SmPC and packaging materials provide respective details and contact information. Kite further gives 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.

11.1. Kite Reporting Requirements to Regulatory Authorities

Kite is responsible for analyzing spontaneous reports of all safety information received independently from this study and reporting to regulatory agencies as determined by country-specific legislation or regulations.

11.2. Definitions

11.2.1. 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 consent form is signed. These are considered to be preexisting conditions and should be documented on the medical history CRF (if applicable).

11.2.2. 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 primary objective: secondary malignancies, CRS, neurologic toxicities, prolonged cytopenia, serious infections, and hypogammaglobulinemia. As part of the primary objective, pregnancy outcomes in female patients of childbearing potential are also of special interest.

11.2.3. 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.

11.2.4. 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.

11.2.5. Serious Adverse Drug Reaction

A SADR is defined as any SAE that is considered causally related to the medicinal product at any dose administered.

11.2.6. 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 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, 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 (e.g., the elderly).
- 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.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Study Report and Publications

12.1.1. 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 YESCARTA within 30 days (45 days for the first report). Two quarterly reports will be submitted as appendices to the PSUR to the PRAC. In case an intervening quarterly report identifies a major new safety finding, the respective report will be submitted promptly as stand-alone document. A particular focus are the Adverse Events of Special Interest (AESIs) which are considered to be the events which are the focus of the primary objective (please see below and in section 11.2.2) 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 primary objectives of the PASS study:
  secondary malignancies, CRS, neurologic toxicities, prolonged cytopenia, serious infections, hypogammaglobulinemia
- If reported, review of any unexpected events, which do not fall under the previously recognized risks or ADRs of special interest
- Review of pregnancies and outcomes
- Summary and conclusions

12.1.2. Annual Reports

Annual reports will be prepared for the first five years and then bi-annually, in which an analysis of treated patients for the primary and secondary endpoints will be included. The versions of the EBMT Cellular and Gene Therapy Form utilized in the EBMT Registry during the respective time period will be provided as appendices to these reports. 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 9.2).

Based upon the approved reports, Kite will submit information to regulatory agencies in accordance with any agreements/commitments.

12.1.3. Final Report

Following the final data analysis, Kite and EBMT will together prepare an appropriate final report, which will be reviewed and approved by the Study Committee and submitted to the Regulatory authorities as applicable by Kite as the study sponsor.

12.1.4. Publications, Conference Abstracts, and Manuscripts

All proposed publications and conference presentations arising from the study will be submitted to the Study Committee for review prior to submission. Both EBMT and Kite will share responsibilities in the development of the statistical analysis plan, data analysis, and 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 to the EMA and the competent authorities of the Member States in which the product is authorized the final manuscript within two weeks after first acceptance for publication.

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14. APPENDICES

Annex 1. List of Stand-Alone Documents
Annex 2. ENCePP Checklist for Study Protocols
Annex 3. Reference Safety Information
Annex 4. Kite Signature Page
Annex 5. Cellular and Gene Therapy Form

Annex 1. List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
1	None	[DD Month YYYY]	[Enter Text]
2	[Number]	[DD Month YYYY]	[Enter Text]
3	[Number]	[DD Month YYYY]	[Enter Text]

Annex 2. ENCePP Checklist for Study Protocols

Study title:
LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF YESCARTA FOR TREATMENT OF RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA AND PRIMARY MEDIASTINAL B-CELL LYMPHOMA

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?	☐	☐	☒	

[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 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

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))	☐	☐	☒	
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)	☐	☐	☒	
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:

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)	☐	☒	☐	
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)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 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?	☐	☒	☐	
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?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

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)	☐	☒	☐	
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)	☐	☒	☐	

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?	☐	☐	☒	

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: PPD

Date: 15 / Nov / 2019

Signature: PPD

Annex 3. Reference Safety Information

Current version of the EU SmPC for YESCARTA®.

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

YESCARTA 0.4 – 2 x 10^8 cells dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

YESCARTA (axicabtagene ciloleucel) is a CD19-directed genetically modified autologous T cell immunotherapy. To prepare YESCARTA, patient's own T cells are harvested and genetically modified *ex vivo* by retroviral transduction to express a chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment linked to CD28 co-stimulatory domain and CD3-zeta signalling domain. The anti-CD19 CAR-positive viable T cells are expanded and infused back into the patient, where they can recognise and eliminate CD19-expressing target cells.

2.2 Qualitative and quantitative composition

Each patient specific single infusion bag of YESCARTA 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 T cells.

Excipients with known effect

Each bag of YESCARTA contains 300 mg sodium.

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

YESCARTA is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

4.2 Posology and method of administration

YESCARTA must be administered in a qualified clinical setting.

YESCARTA therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with YESCARTA. A minimum of four doses of

tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion of YESCARTA.

Posology

YESCARTA is intended for autologous use only (see section 4.4).

A single dose of YESCARTA contains 2 x 10^6 CAR-positive viable T cells per kg of body weight (or maximum of 2 x 10^8 CAR-positive viable T cells for patients 100 kg and above) in approximately 68 mL dispersion in an infusion bag.

The availability of YESCARTA must be confirmed prior to starting the lymphodepleting regimen.

Pre-treatment (lymphodepleting chemotherapy)

- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m^2 intravenous and fludarabine 30 mg/m^2 intravenous should be administered on the 5^{th}, 4^{th}, and 3^{rd} day before infusion of YESCARTA.

Pre-medication

- Paracetamol 500-1,000 mg given orally and diphenhydramine 12.5 to 25 mg intravenous or oral (or equivalent) approximately 1 hour before YESCARTA infusion is recommended.
- Prophylactic use of systemic corticosteroids is not recommended as it may interfere with the activity of YESCARTA.

Monitoring

- 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 or 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 of a qualified clinical facility for at least 4 weeks following infusion.

Special populations

Patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection
There is no clinical experience in patients with active HIV, HBV or HCV infection.

Paediatric population
The safety and efficacy of YESCARTA in children and adolescents below 18 years of age have not yet been established. No data are available.

Elderly
No dose adjustment is required in patients ≥ 65 years of age. Efficacy was consistent with the overall treated patient population.

Method of administration

YESCARTA is to be administered via intravenous infusion.

YESCARTA 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 YESCARTA should take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases.

Preparation of YESCARTA
- Verify that the patient's identity (ID) matches the patient identifiers on the YESCARTA cassette.
- The YESCARTA bag must not be removed from the cassette if the information on the patient-specific label does not match the intended patient.
- Once the patient ID is confirmed, remove the YESCARTA bag from the cassette.
- Check that the patient information on the cassette label matches that on the bag label.
- Inspect the product bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines (or immediately contact Kite).
- Place the infusion bag inside a second sterile bag per local guidelines.
- Thaw YESCARTA 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. YESCARTA 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, YESCARTA is stable at room temperature (20 °C-25 °C) for up to 3 hours.

Administration
- For autologous 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 of YESCARTA.
- Verify the patient ID again to match the patient identifiers on the YESCARTA bag.
- Prime the tubing with 0.9% sodium chloride solution (0.154 mmol sodium per mL) prior to infusion.
- Infuse the entire content of the YESCARTA bag within 30 minutes by either gravity or a peristaltic pump. YESCARTA is stable at room temperature for up to 3 hours after thaw.
- Gently agitate the bag during YESCARTA infusion to prevent cell clumping.
- After the entire content of the bag is infused, rinse the tubing at the same infusion rate with 0.9% sodium chloride solution (0.154 mmol sodium per mL) to ensure all YESCARTA is delivered.

For special precautions for disposal, 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

General

Due to the risks associated with YESCARTA 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.
- Active graft-versus-host disease (GVHD).

Patients treated with YESCARTA should not donate blood, organs, tissues, and cells for transplantation.

YESCARTA is intended solely for autologous use and must not be administered to other patients. Before infusion, the patient's identity must match the patient identifiers on the YESCARTA infusion bag and cassette. Do not infuse YESCARTA if the information on the patient-specific label does not match the intended patient.

Concomitant disease

Patients with active CNS disorder or inadequate renal, hepatic, pulmonary, or cardiac function are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

Primary central nervous system (CNS) lymphoma

There is no experience of use of YESCARTA in patients with primary CNS lymphoma. Therefore, the risk/benefit of YESCARTA has not been established in this population.

Cytokine release syndrome

Nearly all patients experienced some degree of CRS. Severe CRS, including life-threatening and fatal reactions, was very commonly observed with YESCARTA with a time to onset of 1 to 12 days (see section 4.8).

Ensure that a minimum of 4 doses of tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, are available for each patient prior to infusion of YESCARTA.

Monitor patients daily for signs and symptoms of CRS for at least 10 days following infusion at the qualified clinical facility. After the first 10 days following infusion, the patient should be monitored at the physician's discretion.

Counsel patients to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS occur. Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients on YESCARTA. These include the use of tocilizumab or tocilizumab and corticosteroids for moderate, severe, or life-threatening CRS 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.

YESCARTA should not be administered to patients with active infections or inflammatory disease until these conditions have resolved.

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.

Diagnosis of CRS requires excluding alternate causes of systemic inflammatory response, including infection. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

Evaluation for haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) should be considered in patients with severe or unresponsive CRS.

YESCARTA continues to expand and persist following administration of tocilizumab and corticosteroids. Tumour necrosis factor (TNF) antagonists are not recommended for management of YESCARTA-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).	N/A	N/A
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.	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.
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). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days. If not improving, manage as Grade 4 (below).
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 improves, then manage as above. Consider alternate immunosuppressants if no improvement or if condition worsens.

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 have been very commonly observed in patients treated with YESCARTA, which could be life-threatening or fatal (see section 4.8). Patients with a history of CNS disorders such as seizures or cerebrovascular ischaemia may be at increased risk. Fatal and serious cases of cerebral oedema have been reported in patients treated with YESCARTA. Patients should be monitored for signs and symptoms of neurologic adverse reactions (Table 2). Patients should be monitored at least daily for 10 days at the qualified healthcare facility following infusion for signs and symptoms of neurologic toxicity. After the first 10 days following the infusion, the patient should be monitored at the physician's discretion. Counsel patients to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion and to seek immediate medical attention should

signs or symptoms of neurologic toxicity occur. Monitoring of vital signs and organ functions should be considered depending on the severity of the reaction.

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 YESCARTA. 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 per Table 1 for management of Grade 2 CRS. If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 3	Administer tocilizumab 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 over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab 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 improves, then manage as above.	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

Infections and febrile neutropenia

Serious infections have been very commonly observed with YESCARTA (see section 4.8). Patients should be monitored for signs and symptoms of infection before, during, and after YESCARTA infusion and treated appropriately. Prophylactic anti-microbials should be administered according to standard institutional guidelines.

Febrile neutropenia has been observed in patients after YESCARTA 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.

HBV reactivation

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against B cells. Screening for HBV, HCV, and HIV should be performed in accordance with clinical guidelines before collection of cells for manufacturing of YESCARTA.

Prolonged cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. Grade 3 or higher prolonged cytopenias following YESCARTA infusion occurred very commonly and included thrombocytopenia, neutropenia, and anaemia. Monitor blood counts after YESCARTA infusion.

Hypogammaglobulinaemia

B-cell aplasia leading to hypogammaglobulinaemia can occur in patients receiving treatment with YESCARTA. Hypogammaglobulinaemia has been very commonly observed in patients treated with YESCARTA. Immunoglobulin levels should be monitored after treatment with YESCARTA and managed using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement.

Hypersensitivity reactions

Allergic reactions may occur with the infusion of YESCARTA. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA.

Secondary malignancies

Patients treated with YESCARTA may develop secondary malignancies. Monitor patients life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact the company 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 YESCARTA infusion. Signs and symptoms of TLS should be monitored and events managed according to standard guidelines.

Prior treatment with anti-CD19 therapy

There is limited experience with YESCARTA in patients exposed to prior CD19-directed therapy. YESCARTA is not recommended if the patient has relapsed with CD19-negative disease after prior anti-CD19 therapy.

Excipients

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 with YESCARTA.

Live vaccines

The safety of immunisation with live viral vaccines during or following YESCARTA 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 YESCARTA treatment, and until immune recovery following treatment with YESCARTA.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

The pregnancy status of women of child bearing potential must be verified before starting YESCARTA 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 YESCARTA.

Pregnancy

There are no available data with YESCARTA use in pregnant women. No reproductive and developmental toxicity animal studies have been conducted with YESCARTA to assess whether it can cause foetal harm when administered to a pregnant woman (see section 5.3).

It is not known if YESCARTA 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, YESCARTA 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 YESCARTA therapy should be discussed with the treating physician.

Assessment of immunoglobulin levels and B-cells in newborns of mothers treated with YESCARTA should be considered.

Breast-feeding

It is unknown whether YESCARTA 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 YESCARTA 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

YESCARTA 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 refrain from driving or operating 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 YESCARTA in ZUMA-1, a Phase 1/2 study in which 108 patients with relapsed/refractory B-cell non-Hodgkin lymphoma (NHL) received CAR-positive T cells based on a recommended dose which was weight-based. The median duration of follow up was 27.4 months.

The most significant and frequently occurring adverse reactions were CRS (93%), encephalopathy (58%), and infections (39%).

Serious adverse reactions occurred in 56% of patients. The most common serious adverse reactions included encephalopathy (22%), unspecified pathogen infections (16%), bacterial infections (6%), febrile neutropenia (6%), viral infections (5%), and pyrexia (5%).

The most common Grade 3 or higher adverse reactions included encephalopathy (31%), unspecified pathogen infections (19%), CRS (11%), bacterial infection (9%), aphasia (7%), viral infection (6%), delirium (6%), hypotension (6%), and hypertension (6%).

Tabulated list of adverse reactions

Adverse reactions reported are presented below. 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); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse drug reactions identified with YESCARTA

System Organ Class (SOC)	**Frequency**	**Adverse reactions**
Infections and infestations		
	Very common	Unspecified pathogen infections Viral infections Bacterial infections
	Common	Fungal infections
Blood and lymphatic system disorders		
	Very common	Leukopenia Neutropenia Anaemia Thrombocytopenia
	Common	Coagulopathy
Immune system disorders		
	Very common	Cytokine Release Syndrome Hypogammaglobulinaemia
	Common	Hypersensitivity Histiocytosis Haematophagic
Metabolism and nutrition disorders		
	Very common	Dehydration Decreased appetite Hypophosphataemia Hyponatraemia Weight decrease
	Common	Hypocalcaemia Hypoalbuminaemia
Psychiatric disorders		
	Very common	Delirium Anxiety
	Common	Insomnia
Nervous system disorders		
	Very common	Encephalopathy Headache Tremor Dizziness Aphasia
	Common	Ataxia Neuropathy Seizure Dyscalculia Myoclonus
Cardiac disorders		
	Very common	Tachycardia

System Organ Class (SOC)	Frequency	Adverse reactions
		Arrhythmia
	Common	Cardiac arrest Cardiac failure
Vascular disorders		
	Very common	Hypotension Hypertension
	Common	Thrombosis Capillary leak syndrome
Respiratory, thoracic and mediastinal disorders		
	Very common	Cough Dyspnoea Hypoxia Pleural effusion
	Common	Pulmonary oedema
Gastrointestinal disorders		
	Very common	Diarrhoea Nausea Vomiting Constipation Abdominal pain Dry mouth
Skin and subcutaneous tissue disorders		
	Common	Rash
Musculoskeletal and connective tissue disorders		
	Very common	Motor dysfunction Pain in extremity Back pain Arthralgia Muscle pain
Renal and urinary disorders		
	Common	Renal insufficiency
General disorders and administration site conditions		
	Very common	Fatigue Pyrexia Oedema Chills
Investigations		
	Very common	Alanine aminotransferase increased Aspartate aminotransferase increased
	Common	Bilirubin increased

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**.**

Description of selected adverse reactions

Cytokine release syndrome
CRS occurred in 93% of patients. Eleven percent (11%) of patients experienced Grade 3 or higher (severe, life-threatening, and fatal) CRS. The median time to onset was 2 days (range: 1 to 12 days) and the median duration was 7 days (range: 2 to 29 days). Ninety-eight percent (98%) of patients recovered from CRS.

The most common signs or symptoms associated with CRS included pyrexia (83%), hypotension (44%), tachycardia (24%), hypoxia (23%), and chills (20%). Serious adverse reactions that may be associated with CRS included acute kidney injury, atrial fibrillation, ventricular tachycardia, cardiac arrest, cardiac failure, capillary leak syndrome, hypotension, hypoxia, and HLH/MAS. See section 4.4 for monitoring and management guidance.

Neurologic adverse reactions

Neurologic adverse reactions occurred in 67% of patients. Thirty-two percent (32%) of patients experienced Grade 3 or higher (severe or life-threatening) adverse reactions. The median time to onset was 5 days (range: 1 to 17 days). The median duration was 13 days (range: 1 to 191 days). Most patients recovered from neurologic adverse reactions, with the exception of 4 patients who had ongoing neurologic adverse reactions at the time of death; the deaths were due to other causes.

The most common signs or symptoms associated with neurologic adverse reactions included encephalopathy (58%), headache (40%), tremor (31%), dizziness (21%), aphasia (18%), and delirium (17%). Serious adverse reactions including encephalopathy (22%), aphasia (4%), delirium (4%), and seizures (1%) have been reported in patients administered YESCARTA. See section 4.4 for monitoring and management guidance.

Febrile neutropenia and infections
Febrile neutropenia was observed in 36% of patients after YESCARTA infusion. Infections occurred in 39% of patients in ZUMA-1. Grade 3 or higher (severe, life-threatening, or fatal) infections occurred in 26% of patients. Grade 3 or higher unspecified pathogen, bacterial, and viral infections occurred in 19%, 9%, and 6% of patients respectively. The most common site of infection was in the respiratory tract. See section 4.4 for monitoring and management guidance.

Prolonged cytopenias
Grade 3 or higher neutropenia (including febrile neutropenia), anaemia, and thrombocytopenia occurred in 80%, 45%, and 40% of patients, respectively. Prolonged (still present at Day 30 or with an onset at Day 30 or beyond) Grade 3 or higher neutropenia, thrombocytopenia, and anaemia occurred in 26%, 24%, and 10% of patients, respectively. Grade 3 or higher neutropenia, thrombocytopenia, and anaemia present after Day 93 occurred in 11%, 7%, and 3% of patients, respectively. See section 4.4 for management guidance.

Hypogammaglobulinaemia
In ZUMA-1, hypogammaglobulinaemia occurred in 16% of patients. Cumulatively, 33 (31%) of 108 subjects received intravenous immunoglobulin therapy at the time of the 24-month analysis. See section 4.4 for management guidance.

Immunogenicity

The immunogenicity of YESCARTA 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. Three patients tested positive for anti-FMC63 prior to being treated with YESCARTA. An impact of these antibodies on efficacy or safety was not discernible.

Special population

There is limited experience with YESCARTA in patients ≥ 75 years of age. Generally, safety and efficacy were similar between patients ≥ 65 years and patients < 65 years of age treated with YESCARTA. Outcomes were consistent between patients with Eastern Cooperative Oncology Group (ECOG) of 0 and 1 and by sex.

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 YESCARTA.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: not yet assigned

Mechanism of action

YESCARTA, an engineered autologous T-cell immunotherapy product, binds to CD19 expressing cancer cells and normal B cells. Following anti-CD19 CAR T-cell engagement with CD19 expressing target cells, the CD28 and CD3-zeta co-stimulatory domains 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 apoptosis and necrosis of CD19-expressing target cells.

Pharmacodynamic effects

In phase 2 of ZUMA-1, after YESCARTA 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, IFN-γ, and IL2Rα were analyzed. Peak elevation was observed within the first 14 days after infusion, and levels generally returned to baseline within 28 days.

Due to the on-target, off-tumour effect of YESCARTA, a period of B-cell aplasia is expected following treatment. Among 73 patients with evaluable samples at baseline, 40% had detectable B-cells; the B-cell aplasia observed in the majority of patients at baseline was attributed to prior therapies. Following YESCARTA treatment, the proportion of patients with detectable B-cells decreased: 20% had detectable B-cells at Month 3, and 22% had detectable B-cells at Month 6. The initiation of B-cell recovery was first noted at Month 9, when 56% of patients had detectable B-cells. This trend of B-cell recovery continued over time, as 64% of patients had detectable B-cells at Month 18, and 77% of patients had detectable B-cells at Month 24. Patients were not required to be followed after they progressed; thus, the majority of patients with evaluable samples were responders.

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 IL-15, as well as IL-6, were associated with Grade 3 or higher neurologic adverse reactions and Grade 3 or higher CRS.

Clinical efficacy and safety

DLBCL, PMBCL and DLBCL arising from follicular lymphoma (ZUMA-1)
A total of 108 patients were treated with YESCARTA in a phase 1/2 open-label, multicentre, single-arm study in patients with relapsed or refractory aggressive B-cell NHL. Efficacy was based on 101 patients in phase 2, including histologically confirmed DLBCL (N = 77), PMBCL (N = 8), or DLBCL arising from follicular lymphoma, (N = 16) based on the 2008 WHO-classification. DLBCL in ZUMA-1 included patients with DLBCL NOS, other DLBCL subtypes, and high-grade B-cell lymphoma (HGBCL) based on the 2016 WHO-classification. Forty-seven patients were evaluable for MYC, BCL-2, and BCL-6 status. Thirty were found to have double expressor DLBCL (overexpression of both MYC and BCL-2 protein); 5 were found to have HGBCL with MYC, BCL-2 or BCL-6 gene rearrangement (double- and triple-hit); and 2 were found to have HGBCL not otherwise specified. Sixty-six patients were evaluable for cell-of-origin classifications (germinal center B-cell type [GCB] or activated B-cell type [ABC]). Of these, 49 patients had GCB-type and 17 patients had ABC-type.

Eligible patients were ≥ 18 years of age with refractory disease defined as progressive disease (PD) or stable disease (SD) as best response to last line of therapy, or disease progression within 12 months

after autologous stem cell transplant (ASCT). Patients who were refractory to chemotherapy or who relapsed after two or more lines of systemic therapy were generally ineligible for haematopoietic stem cell transplantation. Patients must have received at least prior anti-CD20 antibody therapy and an anthracycline containing regimen. Patients with CNS lymphoma, a history of allogeneic stem cell transplantation (SCT) or prior anti-CD19 CAR or other genetically modified T-cell therapy were excluded. Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia), cardiac ejection fraction of less than 50% or room air oxygen saturation of less than 92%, or autoimmune disease requiring systemic immunosuppression were ineligible. The median duration of follow up was 27.1 months (still ongoing). A summary of the patient demographics is provided in Table 4.

Table 4: Summary of demographics for ZUMA-1 phase 2 (12 month analysis)

Category	**All leukapheresed (ITT) Cohort 1 + 2 (N = 111)**	**All treated (mITT) Cohort 1 + 2 (N = 101)**
Age (years)		
Median (min, max)	58 (23, 76)	58 (23, 76)
≥ 65	23%	24%
Male gender	69%	67%
Race		
White	85%	86%
Asian	4%	3%
Black	4%	4%
ECOG status		
ECOG 0	41%	42%
ECOG 1	59%	58%
Median number of prior therapies (min, max)	3 (1, 10)	3 (1, 10)
Patients with refractory disease to ≥ 2 prior lines of therapy	77%	76%
Patients relapsed within 1 year of ASCT	20%	21%
Patients with International Prognostic Index 3/4	46%	46%
Patients with disease stage III/IV	85%	85%

YESCARTA was administered as a single infusion at a target dose of 2×10^6 anti-CD19 CAR T cells/kg after lymphodepleting chemotherapy regimen of 500 mg/m^2 intravenous cyclophosphamide and 30 mg/m^2 intravenous fludarabine on the 5th, 4th, and 3rd day before YESCARTA. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was not permitted. All patients were hospitalized for observation for a minimum of 7 days after YESCARTA infusion.

Of 111 patients who underwent leukapheresis, 101 received YESCARTA. Nine patients were not treated, primarily due to progressive disease or serious adverse events after enrolment and prior to cell delivery. One out of 111 patients did not receive the product due to manufacturing failure. The median time from leukapheresis to product delivery was 17 days (range: 14 to 51 days), and the median time from leukapheresis to infusion was 24 days (range: 16 to 73 days). The median dose was 2.0×10^6 anti-CD19 CAR T cells/kg. ITT was defined as all patients who underwent leukapheresis; mITT was defined as all patients who received YESCARTA.

The primary endpoint was objective response rate (ORR). Secondary endpoints included duration of response (DOR), overall survival (OS), and severity of adverse events. The ORR was prespecified to be tested in the first 92 treated patients and was significantly higher than the prespecified rate of 20% ($P < 0.0001$).

In the primary analysis, based on the mITT population (minimum follow up of 6 months) the ORR was 72% and the complete response (CR) rate was 51%, as determined by an independent review committee. In the 12-month follow-up analysis (Table 5), the ORR was 72% and the CR rate was

51%. The median time to response was 1.0 months (range: 0.8 to 6.3 months). The DOR was longer in patients who achieved CR, as compared to patients with a best response of partial response (PR). Of the 52 patients who achieved CR, 7 patients had SD and 9 had PR at their initial tumour assessment and converted to CR as late as 6.5 months. The ORR results within PMBCL and DLBCL arising from follicular lymphoma were both 88%. CR rates were 75% and 56%, respectively. Of the 111 patients in the ITT population, the ORR was 66% and the CR was 47%. Other outcomes were consistent with those of the mITT population.

In the 24-month follow-up analysis, based on the mITT population (results from an independent review committee), the ORR and the CR rate were 74% and 54%, respectively. The median time to response was 1.0 months (range: 0.8 to 12.2 months). The DOR was longer in patients who achieved CR compared to patients with a best response of PR (Table 5). Of the 55 patients who achieved CR, 7 patients had SD and 10 had PR at their initial tumour assessment and converted to CR as late as 12 months after YESCARTA infusion. Median duration of response and median overall survival have not been reached (Table 5).

In the phase 1 part of ZUMA-1, 7 patients were treated. Five patients responded, including 4 CRs. At the 12-month follow-up analysis, 3 patients remained in CR 24 months after YESCARTA infusion. At the 24-month follow-up analysis, these 3 patients remained in CR at 30 to 35 months after YESCARTA infusion.

Table 5. Summary of efficacy results for ZUMA-1 phase 2

Category	**All leukapheresed (ITT) Cohort 1 + 2 (N = 111)**		**All treated (mITT) Cohort 1 + 2 (N = 101)**	
	12-month analysis	**24-month analysis**	**12-month analysis**	**24-month analysis**
ORR (%) [95% CI]	66 (56, 75)	68 (58, 76)	72 (62, 81)	74 (65, 82)
CR (%)	47	50	51	54
Duration of Response[a], median (range) in months	14.0 (0.0, 17.3)	NE (0.0, 29.5)	14.0 (0.0, 17.3)	NE (0.0, 29.5)
Duration of Response[a], CR, median (range) in months	NE (0.4, 17.3)	NE (0.4, 29.5)	NE (0.4, 17.3)	NE (0.4, 29.5)
Overall Survival, median (months) [95% CI]	17.4 (11.6, NE)	17.4 (11.6, NE)	NE (12.8, NE)	NE (12.8, NE)
6 month OS (%) [95% CI]	81.1 (72.5, 87.2)	81.1 (72.5, 87.2)	79.2 (69.9, 85.9)	79.2 (69.9, 85.9)
9 month OS (%) [95% CI]	69.4 (59.9, 77.0)	69.4 (59.9, 77.0)	69.3 (59.3, 77.3)	69.3 (59.3, 77.3)
12 month OS (%) [95% CI]	59.3 (49.6, 67.8)	59.5 (49.7, 67.9)	60.4 (50.2, 69.2)	60.4 (50.2, 69.2)
24 month OS (%) [95% CI]	Not applicable	47.7 (38.2, 56.7)	Not applicable	50.5 (40.4, 59.7)

NE= Not estimable (not reached)

a Duration of response was censored at the time of SCT for subjects who received SCT while in response.

Note: The 12-month analysis had a median follow-up of 15.1 months. The 24-month analysis had a median follow-up of 27.1 months. OS relates to the time from the leukapheresis date (ITT) or YESCARTA infusion (mITT) to death from any cause.

SCHOLAR-1
A retrospective, patient-level, pooled analysis of outcomes in refractory aggressive NHL (N = 636) was conducted (Crump et al., 2017) to provide confirmation of the prespecified control response rate of 20% and historical context for interpreting the ZUMA-1 results. The analysis included patients who had not responded (SD or PD) to their last line of therapy, or had relapsed within 12 months after ASCT. Response and survival after treatment with available standard-of-care therapy was evaluated. The ORR was 26% [95% CI (21, 31)] and the CR rate was 7% [95% CI (3, 15)], with a median OS of 6.3 months.

5.2 Pharmacokinetic properties

Peak levels of anti-CD19 CAR T cells occurred within the first 8 to 15 days after YESCARTA infusion. The median peak level of anti-CD19 CAR T cells in the blood (C_{max}) was 38.3 cells/µL (range: 0.8 to 1513.7 cells/µL), which decreased to a median of 2.1 cells/µL by 1 month (range: 0 to 167.4 cells/µL) and to a median of 0.4 cells/µL by 3 months (range: 0 to 28.4 cells/µL) after YESCARTA infusion.

Age (range: 23 to 76 years) and sex had no significant impact on AUC and C_{max} of YESCARTA.

The number of anti-CD19 CAR T cells in the blood was positively associated with objective response (CR or PR). The median anti-CD19 CAR T cell C_{max} level in responders (N = 71) was 216% higher compared to the corresponding level in nonresponders (N = 25) (43.6 cells/µL *versus* 20.2 cells/µL). Median $AUC_{Day\ 0\text{-}28}$ in responding patients (N = 71) was 253% of the corresponding level in nonresponders (N = 25) (562.0 days x cells/µL *versus* 222.0 days x cells/µL).

YESCARTA comprises human autologous T cells. The anticipated metabolic products are typical cellular degradation products resulting from normal cellular clearance mechanisms. Thus, the infused CAR T cells are expected to be cleared over time. Anti-CD19 CAR T cell levels decreased toward background levels by Month 3 after infusion.
Studies of YESCARTA in patients with hepatic and renal impairment were not conducted.

5.3 Preclinical safety data

YESCARTA 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 drug development were not performed.

No carcinogenicity or genotoxicity studies have been conducted with YESCARTA.

No studies have been conducted to evaluate the effects of YESCARTA 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

YESCARTA is stable for 1 year when stored frozen in the vapour phase of liquid nitrogen (≤ -150 ˚C).

The stability of YESCARTA upon completion of thawing is up to 3 hours at room temperature (20 ˚C to 25 °C). However, YESCARTA infusion should begin within 30 minutes of thaw completion and the total YESCARTA infusion time should not exceed 30 minutes. Thawed product should not be refrozen.

6.4 Special precautions for storage

YESCARTA bags must be stored in the vapour phase of liquid nitrogen (≤ -150 ˚C) and YESCARTA must remain frozen until the patient is ready for treatment to ensure viable live autologous cells are administered to the patient.

For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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 cassette.

6.6 Special precautions for disposal and other handling

Irradiation could lead to inactivation of the product.

Precautions to be taken for the disposal of the medicinal product

YESCARTA contains genetically modified human blood cells. Local biosafety guidelines should be followed for unused medicinal products or waste material. All material that has been in contact with YESCARTA (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local biosafety guidelines.

7. MARKETING AUTHORISATION HOLDER

Kite Pharma EU B.V.
PPD

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1299/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 August 2018

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 OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER 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

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Kite Pharma, Inc.
PPD

Name and address of the manufacturer responsible for batch release

Lonza Netherlands B.V.
PPD

Kite Pharma EU B.V.
PPD

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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**

The requirements for submission of periodic safety update reports 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 shall submit the first periodic safety update report 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 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 YESCARTA, the MAH must ensure that hospitals and their associated centres that dispense YESCARTA are specially qualified in accordance with the agreed control distribution program.

The MAH must ensure on-site, immediate access to 4 doses of tocilizumab for each patient as CRS management medication prior to treating patients.

YESCARTA will only be supplied to hospitals and associated centres that are qualified and only if the healthcare professionals involved in the treatment of a patient have completed the educational program.

Educational program – Prior to the launch of YESCARTA 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 YESCARTA is marketed, all HCPs who are expected to prescribe, dispense, and administer YESCARTA shall be provided with a guidance document to:

- facilitate identification of CRS and serious neurologic adverse reactions
- facilitate management of the CRS and serious neurologic adverse reactions
- ensure adequate monitoring of CRS and serious neurologic adverse reactions
- facilitate provision of all relevant information to patients
- ensure that adverse reactions are adequately and appropriately reported
- ensure that detailed instructions about the thawing procedure are provided
- before treating a patient, ensure that 4 doses of tocilizumab for each patient are available on site

Patient Educational program

To inform and explain to patients

- the risks of CRS and serious neurologic adverse reactions, associated with YESCARTA
- the need to report the symptoms to their treating doctor immediately
- the need to remain in the proximity of the location where YESCARTA was received for at least 4 weeks following YESCARTA 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
Non-interventional post-authorisation safety study (PASS): In order to assess the safety profile including long term safety in patients with B-lymphocyte malignancies treated with axicabtagene ciloleucel in the post marketing setting, the applicant should conduct and submit a study based on a registry.	•Update reports: Annual safety reports and 5-yearly interim reports •Final report of study results: December 2038

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CONTAINER (CASSETTE)

1. NAME OF THE MEDICINAL PRODUCT

YESCARTA 0.4 – 2 x 10^8 cells dispersion for infusion
axicabtagene ciloleucel (CAR+ viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor (CAR) with a target dose of 2 x 10^6 anti-CD19 CAR-positive viable T cells/kg.

3. LIST OF EXCIPIENTS

Excipients: Cryostor CS10, human albumin, sodium chloride. See leaflet for further information.

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

This medicine contains genetically-modified cells.
Unused medicine must be disposed of in compliance with the local biosafety guidelines.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kite Pharma EU B.V.
PPD

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1299/001

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

YESCARTA 0.4 – 2 x 10^8 cells dispersion for infusion
axicabtagene ciloleucel (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

One sterile infusion bag.
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

YESCARTA 0.4 – 2 x 10^8 cells dispersion for infusion
axicabtagene ciloleucel (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 YESCARTA is and what it is used for
2. What you need to know before you are given YESCARTA
3. How YESCARTA is given
4. Possible side effects
5. How to store YESCARTA
6. Contents of the pack and other information

1. What YESCARTA is and what it is used for

YESCARTA is a type of medicine called a “genetically modified cell therapy”.

YESCARTA is made specially for you as a single administration of your own modified white blood cells. It is given by a drip (*infusion*) into a vein (*intravenously*).

It is used to treat aggressive conditions in adults with diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) affecting your lymph tissue (part of the immune system) that affects a type of white blood cell called B lymphocytes and other organs in your body. Too many of these abnormal white blood cells accumulate in your tissue and this is the cause of the symptoms you may have. It is used to treat these conditions when other available medicines have stopped working for you.

2. What you need to know before you are given YESCARTA

You should not be given YESCARTA 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.

Warnings and precautions

YESCARTA is made from your own white blood cells and should only be given to you.

Before you are given YESCARTA you should tell your doctor if you:
- have problems with your nervous system (such as fits, stroke, or memory loss).
- have kidney problems.

- have low blood cell levels (blood counts).
- have had a stem cell transplant in the last 4 months.
- have any lung, heart or blood pressure (low or raised) problems.
- have signs or symptoms of graft-versus-host disease. This happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhoea and bloody stools.
- notice the symptoms of your cancer are getting worse. If you have lymphoma this might include fever, feeling weak, night sweats, sudden weight loss.
- have an infection. The infection will be treated before the YESCARTA infusion.
- have had hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection.

If any of the above apply to you (or you are not sure), talk to your doctor before being given YESCARTA.

Tests and checks
Before you are given YESCARTA your doctor will:
- Check your lungs, heart and blood pressure.
- Look for signs of infection; any infection will be treated before you are given YESCARTA.
- Check if your cancer is getting worse.
- Look for signs of graft-versus-host disease that can happen after a transplant.
- 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.

After you have been given YESCARTA
Tell your doctor or nurse immediately if you have any of the following:
- Chills, extreme tiredness, weakness, dizziness, headache, cough, shortness of breath, or rapid heartbeat, which may be symptoms of a condition known as cytokine release syndrome. Take your temperature twice a day for 3-4 weeks after treatment with YESCARTA. 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, 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.

Your doctor will regularly check your blood counts as the number of blood cells and other blood components may decrease.

Do not donate blood, organs, tissues or cells for transplants.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before you are given YESCARTA. Your doctor may need to take special care of you during your treatment with YESCARTA.

In some cases, it might not be possible to go ahead with the planned treatment with YESCARTA. For example:

- If YESCARTA infusion is delayed for more than 2 weeks after you have received preparatory chemotherapy you may have to receive more preparative chemotherapy.

Children and adolescents

YESCARTA should not be used in children and adolescents below 18 years of age.

Other medicines and YESCARTA

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

Before you are given YESCARTA 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 YESCARTA.

In particular, you must not be given certain vaccines called live vaccines:
- In the 6 weeks before you are given the short course of chemotherapy (called lymphodepleting chemotherapy) to prepare your body for the YESCARTA cells.
- During YESCARTA 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 YESCARTA 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 YESCARTA, talk to your doctor immediately.
- You will be given a pregnancy test before treatment starts. YESCARTA should only be given if the results show you are not pregnant.

Discuss pregnancy with your doctor if you have received YESCARTA.

Driving and using machines
Some people may feel tired, dizzy or have some shaking after being given YESCARTA. If this happens to you, do not drive or use heavy machines until at least 8 weeks after infusion or until your doctor tells you that you have completely recovered.

YESCARTA contains sodium
This medicine contains 300 mg sodium (main component of cooking/table salt) in each infusion. This is the equivalent to 15% of the recommended maximum daily dietary intake of sodium for an adult.

3. How YESCARTA is given

YESCARTA will always be given to you by a healthcare professional.

- Since YESCARTA 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 frozen and sent away to make YESCARTA. It usually takes about 3 to 4 weeks to receive your YESCARTA therapy but the time may vary.

Medicines given before YESCARTA treatment
During the 30 to 60 minutes before you are given YESCARTA 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.

Prior to receiving YESCARTA, you will be given other medicines such as preparative chemotherapy, which will allow your modified white blood cells in YESCARTA to multiply in your body when the medicine is given to you.

Your doctor or nurse will check carefully that this medicine is yours.

How you are given YESCARTA

- YESCARTA is a one-time treatment. It will not be given to you again.
- Your doctor or nurse will give you a single infusion of YESCARTA into your vein for approximately 30 minutes.
- YESCARTA is the genetically modified version of your white blood cells. Your healthcare professional handling YESCARTA will therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases and will follow local biosafety guidelines to clean up or dispose of any material that has been in contact with YESCARTA.

You must receive YESCARTA infusion in a qualified clinical facility and be discharged only when your doctor thinks it is safe for you to go home.
Your doctor may do blood tests to check for side effects.

After you are given YESCARTA

- Plan to stay within proximity from the hospital where you were treated for at least 4 weeks after you have been given YESCARTA. Your doctor will recommend that you return to the hospital daily for at least 10 days and will consider whether you need to stay at the hospital as an in-patient for the first 10 days after infusion. 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 the qualified clinical facility 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.

YESCARTA can cause side effects to your immune system that may be serious or life-threatening, and can lead to death.

The following side effects have been reported in clinical studies with YESCARTA.

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).
- Fever or chills.
- Decrease in the number of red blood cells (cells that carry oxygen) which may cause you to feel extremely tired with a loss of energy.
- Low blood pressure, dizziness.
- Feeling sick, constipation, diarrhoea, pain in the stomach or being sick.
- Headache, depressed level of consciousness, difficulty in speaking, agitation, shaking.

- Decrease in the number of white blood cells, which are important for fighting infections.
- Decreased levels of sodium, phosphate, or potassium which will show up on blood tests.
- Changes in the rhythm or rate of the heartbeat.
- Anxiety.
- Decrease in the number of cells that help clot the blood (thrombocytopenia).
- Infections in the blood caused by bacteria, viruses or other types of infection.
- Shortness of breath, cough.
- Low levels of antibodies called immunoglobulins, which may lead to infections.
- High blood pressure.
- Swelling in the limbs, fluid around the lungs (pleural effusion).
- Muscle pain, back pain.
- Extreme tiredness.
- Dehydration.

Common (may affect up to 1 in 10 people)

- Difficulty understanding numbers, memory loss, fits, loss of control of body movements.
- Failure of the kidneys causing your body to hold onto fluid which can be serious or life threatening.
- Fluid in the lungs.
- Lung infection.
- Sudden, unexpected stopping of the heart (cardiac arrest); this is serious and life-threatening.
- Heart failure.
- Muscle spasms.
- Leakage of fluids from blood vessels into surrounding tissue. This can lead to a weight gain and difficulty in breathing.
- Decreased levels of calcium which will show up on blood tests.
- Infections in the blood caused by fungi.

Tell your doctor immediately if you get any of the side effects listed above. Do not try to treat your symptoms with other medicines on your own.

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 YESCARTA

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.

Store frozen in vapour phase of liquid nitrogen ≤ -150 °C until thawed for use.
Do not refreeze.

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. This medicine contains genetically modified human blood cells. Local biosafety guidelines should be followed for unused medicine or waste material.

6. Contents of the pack and other information

What YESCARTA contains

The active substance is axicabtagene ciloleucel. 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.
The other ingredients (excipients) are: Cryostor CS10, sodium chloride, human albumin. See section 2 “YESCARTA contains sodium”.

What YESCARTA looks like and contents of the pack

YESCARTA 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.
PPD

Manufacturer
Lonza Netherlands B.V.
PPD

Kite Pharma EU B.V.
PPD

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Gilead Sciences Belgium SPRL-BVBA
Tél/Tel: PPD

България
Gilead Sciences Ireland UC
Тел.: PPD

Česká republika
Gilead Sciences s.r.o.
Tel: PPD

Danmark
Gilead Sciences Sweden AB
Tlf: PPD

Deutschland
Gilead Sciences GmbH
Tel: PPD

Eesti
Gilead Sciences Poland Sp. z o.o.
Tel: PPD

Lietuva
Gilead Sciences Poland Sp. z o.o.
Tel: PPD

Luxembourg/Luxemburg
Gilead Sciences Belgium SPRL-BVBA
Tél/Tel: PPD

Magyarország
Gilead Sciences Ireland UC
Tel: PPD

Malta
Gilead Sciences Ireland UC
Tel: +PPD

Nederland
Gilead Sciences Netherlands B.V.
Tel: PPD

Norge
Gilead Sciences Sweden AB
Tlf: PPD

Ελλάδα
Gilead Sciences Ελλάς Μ.ΕΠΕ.
Τηλ: PPD

España
Gilead Sciences, S.L.
Tel: PPD

France
Gilead Sciences
Tél: PPD

Hrvatska
Gilead Sciences Ireland UC
Tel: PPD

Ireland
Gilead Sciences Ireland UC
Tel: PPD

Ísland
Gilead Sciences Sweden AB
Sími: PPD

Italia
Gilead Sciences S.r.l.
Tel: PPD

Κύπρος
Gilead Sciences Ελλάς Μ.ΕΠΕ.
Τηλ: PPD

Latvija
Gilead Sciences Poland Sp. z o.o.
Tel: PPD

Österreich
Gilead Sciences GesmbH
Tel: PPD

Polska
Gilead Sciences Poland Sp. z o.o.
Tel: PPD

Portugal
Gilead Sciences, Lda.
Tel: PPD

România
Gilead Sciences Ireland UC
Tel: PPD

Slovenija
Gilead Sciences Ireland UC
Tel: PPD

Slovenská republika
Gilead Sciences Slovakia s.r.o.
Tel: PPD

Suomi/Finland
Gilead Sciences Sweden AB
Puh/Tel: PPD

Sverige
Gilead Sciences Sweden AB
Tel: PPD

United Kingdom
Gilead Sciences Ltd
Tel: PPD

This leaflet was last revised in

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:

Preparation of YESCARTA

- Verify that the patient's identity (ID) matches the patient identifiers on the YESCARTA cassette.
- The YESCARTA product bag must not be removed from the cassette if the information on the patient-specific label does not match the intended patient.
- Once the patient's ID is confirmed, remove the YESCARTA product bag from the cassette.
- Check that the patient information on the cassette label matches that on the bag label.
- Inspect the product bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines (or immediately contact Kite).
- Place the infusion bag inside a second sterile bag per local guidelines.
- Thaw YESCARTA 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. YESCARTA 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, YESCARTA is stable at room temperature (20 ˚C-25 ˚C) for up to 3 hours.

Do NOT use a leukodepleting filter.

All material that has been in contact with YESCARTA (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local biosafety guidelines. Accordingly, healthcare professionals should take appropriate precautions (wearing gloves and glasses) when handling leukapheresis material or YESCARTA to avoid potential transmission of infectious diseases. Work surfaces and material which have potentially been in contact with YESCARTA must be decontaminated with appropriate disinfectant.

This medicine contains genetically modified human blood cells. Any unused medicine or waste material must be disposed of in accordance with local biosafety guidelines.

Annex 4. Kite Signature Page

KITE PHARMA INC.

LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF YESCARTA FOR TREATMENT OF RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA AND PRIMARY MEDIASTINAL B-CELL LYMPHOMA

ORIGINAL, 07 FEBRUARY 2019
VERSION 1.1, 03 JULY 2019
VERSION 1.2, 09 OCTOBER 2019
VERSION 1.3, 06 NOVEMBER 2019

This protocol has been approved by Kite Pharma Inc. The following signatures document this approval.

PPD

Kite Study Director (Printed)
Author

PPD

15-Nov 2019
Date

PPD de Bruyn PPD
Kite Gilead EU QPPV (Printed) deputy

PPD

15-Nov-2019
Date

Annex 5. Cellular and Gene Therapy Form

EBMT Cellular and Gene Therapy Form in the version foreseen for provision in the EBMT Registry at time point of MACRO system implementation. During the course of the study updated versions will be provided as appendices of annual reports (see 12.1.2).

Cellular and Gene Therapy Form

Registration at Day 0

CENTRE IDENTIFICATION

EBMT Code (CIC): .... Hospital: ..... Unit: .....

Contact person.....

PATIENT DATA

Date of this Report: ……. - ……. - …….
yyyy *mm* *dd*

EBMT Registry Unique Identification Code (UIC) .....
(if applicable)

Hospital Unique Patient Number or Code (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 ……
(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))

Date of Birth: ..... - ..... - .....
yyyy *mm* dd

Sex: ☐ Male ☐ Female
(at birth)

INDICATION FOR CELL/GENE THERAPY TREATMENT

SELECT ALL THAT APPLY

☐ Treatment of a Primary disease

Date of initial diagnosis: ..... - ..... - .....
yyyy mm dd

INDICATE THE PRIMARY DISEASE OF THE PATIENT WHO RECEIVED THIS THERAPY

- ☐ Primary Acute Leukaemia
  - ☐ Acute myelogenous leukaemia (Page 14)
  - ☐ Precursor lymphoid neoplasms (Page 18)
  - ☐ Other Primary Acute Leukaemia (Page 21)
- ☐ Chronic Leukaemia
  - ☐ Chronic Myeloid Leukaemia (CML) (Page 22)
  - ☐ Chronic Lymphocytic Leukaemia (CLL) (Page 23)
  - ☐ Prolymphocytic Leukaemia (PLL) (Page 24)
- ☐ Lymphoma (Page 25)
  - ☐ Non Hodgkin
  - ☐ Hodgkin's Disease
- ☐ Myelodysplastic syndrome and/or myeloproliferative neoplasm
  - ☐ MDS (Page 30)
  - ☐ MDS/MPN (Page 33)
  - ☐ Myeloproliferative neoplasm (Page 35)
- ☐ Myeloma /Plasma cell disorder (Page 37)
- ☐ Aplastic Anaemia and Other Bone Marrow Failure Syndromes (Page 39)
- ☐ Haemoglobinopathy (Page 39)
- ☐ Solid Tumour (Page 40)
- ☐ Inherited disorders (Page 42)
  - ☐ Primary immune deficiencies
  - ☐ Metabolic disorders
  - ☐ Other (Page 43)
- ☐ Histiocytic disorders (Page 43)
- ☐ Autoimmune disease
  - ☐ Connective (Page 44)
  - ☐ Vasculitis (Page 44)
  - ☐ Arthritis (Page 45)
  - ☐ Neurological (MS, etc) (Page 45)
  - ☐ Haematological (Page 45)
  - ☐ Bowel disorder (Page 46)
  - ☐ Other (Diabetes, etc.) (Page 46)

Other primary disease
☐ Specify .....

Complete and attach the relevant DISEASE CLASSIFICATION SHEET as per the page numbers indicated above, including the date of Cell/Gene therapy and disease status at Cell/Gene therapy, then continue to Clinical setting in the next page.

☐ **Treatment or prevention of complications derived from a previous treatment including HSCT or expected from a subsequent treatment**

Indicate the date of the last HSCT or Cell/Gene therapy for this patient ..... - ..... - ..... ☐ Not applicable
yyyy mm dd

➡ **Please make sure that MedB 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/cell/gene therapy .**

☐ **Other indication, specify**:_____

Please, contact the Registry helpdesk before proceeding: ***registryhelpdesk@ebmt.org***

Previous therapies given before transplant/cell/gene therapy

Has the information requested in this section been submitted with a previous HSCT/Cell/Gene Therapy registration for this patient?

☐ Yes: go to page 5, *"Status at Cell/Gene Therapy"*
☐ No: proceed with this section

Was the patient treated before Cell/Gene Therapy procedure?

☐ No – *Proceed to page 5, STATUS AT CELL/GENE THERAPY*
☐ Yes

☐ Unknown

Chemotherapy/Drugs ☐ No ☐ Yes ☐ Unknown

If yes:

	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
2nd Line			..... - ..... - ..... *yyyy mm dd*	..... - ..... - ..... *yyyy mm dd*	☐ Complete remission ☐ Partial remission (> 50 %) ☐ No response (< 50 %) ☐ Relapse/progression
3rd Line			..... - ..... - ..... *yyyy mm dd*	..... - ..... - ..... *yyyy mm dd*	☐ Complete remission ☐ Partial remission (> 50 %) ☐ No response (< 50 %) ☐ Relapse/progression
4th Line			..... - ..... - ..... *yyyy mm dd*	..... - ..... - ..... *yyyy mm dd*	☐ Complete remission ☐ Partial remission (> 50 %) ☐ No response (< 50 %) ☐ Relapse/progression

Enzyme replacement therapy ☐ No ☐ Yes, specify: ..... ☐ Unknown

Radiotherapy ☐ No ☐ Yes

Other treatment ☐ No ☐ Yes, specify: ..... ☐ Unknown

BASIC INFORMATION ON THE CELL/GENE THERAPY

Clinical setting:
(Select only one)

☐ As per marketing approval / Standard of care / Institutional guidelin s
☐ Hospital exemption
☐ Compassionate use

Is patient enrolled in a IV / PASS study?
☐ No ☐ Yes

☐ Investigational DP / Clinical trial (CT)

Phase ☐ 1 ☐ 1/2 ☐ 2 ☐ 2/3 ☐ 3

Blind trial ☐ No ☐ Yes

Randomised trial ☐ No ☐ Yes

Eudract number…….. USA CT number…… UMIN CT number……
(Japan)

☐ Tick here if you want this registration hidden until ..... - ..... - .....
(indicate by which date the registration can be made available for research) yyyy mm dd

Is the infused Cell/Gene Therapy cellular product a commercial product?

☐ Yes Was the product use consistent with the specification? ☐ Yes ☐ No
☐ No

STATUS AT CELL/GENE THERAPY

PATIENT WEIGHT AT CELL/GENE THERAPY (kg): .....

HEIGHT AT CELL/GENE THERAPY(cm): .....

Performance score of the patient at initiation of treatment

SYSTEM USED *(choose only one)*:

☐ Karnofsky or ☐ Lansky: Score: ☐ 10 ☐ 20 ☐ 30 ☐ 40 ☐ 50 ☐ 60 ☐ 70 ☐ 80 ☐ 90 ☐ 100
☐ ECOG: Score: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

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

Comorbidity	Definitions	No	Yes	Not evaluated
Solid tumour, previously present	Treated at any time point in the patient's past history, excluding non-melanoma skin cancer Indicate type	☐	☐	☐
Inflammatory bowel disease	Crohn's disease or ulcerative colitis	☐	☐	☐
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	☐	☐	☐
Infection	Requiring continuation of antimicrobial treatment after day 0	☐	☐	☐
Diabetes	Requiring treatment with insulin or oral hypoglycaemics but not diet alone	☐	☐	☐
Renal: moderate/severe	Serum creatinine > 2 mg/dL or >177 µmol/L, on dialysis, or prior renal transplantation	☐	☐	☐
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	☐	☐	☐
moderate/ severe	Liver cirrhosis, bilirubin greater than 1.5 × ULN, or AST/ALT greater than 2.5 × ULN	☐	☐	☐
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	☐	☐	☐
Cardiac	Coronary artery disease, congestive heart failure, myocardial infarction, EF ≤ 50%, or shortening fraction in children (<28%)	☐	☐	☐
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	☐	☐	☐
Heart valve disease	Except mitral valve prolapse	☐	☐	☐
Pulmonary: moderate	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	Patients with a body mass index > 35 kg/m2	☐	☐	☐
Peptic ulcer	Requiring treatment	☐	☐	☐
Psychiatric disturbance	Depression or anxiety requiring psychiatric consultation or treatment	☐	☐	☐

Specify other additional ***major*** clinical abnormalities not listed above and present prior to the preparative regimen:

.....

.....

.....

Was B-Cell Aplasia present at the time of treatment? ☐ No ☐ Yes ☐ Not Evaluated
(Not applicable to Stem Cell Gene Therapy)

If yes, % of B-Cells .....

Cell origin

☐ Autologous -> Go to page 8 *CELL/GENE THERAPY INFUSION UNIT*

☐ Allogeneic

This product is manufactured from:

☐ A known donor never used before to treat this patient -> Continue with DONOR section below
(eg. from a Donor registry or related)

☐ A donor that is already registered as part of a previous treatment Donor ID:.....
-> Skip DONOR section and go to CELL/GENE THERAPY INFUSION UNIT

☐ An unknown donor with not available data -> Skip DONOR section and go to CELL/GENE THERAPY INFUSION UNIT
(eg. from a commercial product)

Donor

HLA match type

☐ HLA-identical s bling *(may include non-monozygotic twin)*
☐ Syngeneic *(monozygotic twin)*
☐ HLA-matched other relative
☐ HLA-mismatched relative: Degree of mismatch ☐ 1 HLA locus mismatch
☐ ≥ 2 HLA loci mismatch

Donor ID given by the centre .....

☐ Unrelated donor

ION code of the Donor Registry or Cord Blood Bank (*up to 4 characters*) ....

Name of donor registry or Cord Blood Bank ....

Donor centre name .....
(if applicable, optional)

Donor ID given by the Donor Registry or the Cord Blood Bank listed above .....

Patient ID given by the Donor Registry or the Cord Blood Bank listed above .....
(optional)

Donor information

Date of birth : .... - .... - .... *yyyy mm dd* OR Age at time of donation..... *years* ..... *months*
(if date of birth not provided)

Donor Sex ☐ Male ☐ Female
(at birth)

CELL/GENE THERAPY INFUSION UNIT(S)

Was there more than one cell infusion unit administered during this treatment

☐ No

☐ Yes: Number of different cell infusion units that form part of this treatment .....

Cell/Gene 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**
Enter Hospital name if it isn't a commercial product

Name of the product *(if applicable)* .....

Batch number *(if applicable)* .....

Unique ID of the product *(if applicable)* .....

Identification of the Cell Infusion Unit given by the Centre .....
*This item is **mandatory** if more than one cell infusion unit has been used in the same treatment*

CELL TYPES

☐ Mononuclear cells (DLI)	☐ CD3+ lymphocytes	☐ CD4+ lymphocytes
☐ CD8+ lymphocytes	☐ Gamma-Delta T-cells	☐ Regulatory T-cells
☐ NK cells	☐ Dendritic cells	☐ CD34+
☐ Mesenchymal	☐ Other, specify	

TISSUE SOURCE *(check all that apply)*

☐ Bone Marrow	☐ Peripheral Blood	☐ Umbilical cord Blood
☐ Tumour	☐ Other, specify	

COLLECTION PROCEDURE

Date of the collection ..... - ..... - .....
If more than one collection use the date of the first collecition
yyyy mm dd

Number of collections .....

PERIPHERAL BLOOD MOBILISATION (ONLY WHEN CD34+ WAS SELECTED AS CELL TYPE)

List all drugs: chemotherapy, growth factors, antibodies, etc

Date of 1st aphaeresis after this mobilisation	Number of this mobilisation	Drug name	Drug name	Drug name
..... - ..... - ..... *yyyy mm dd*	.....	.....	.....	.....
		.....	.....	.....
..... - ..... - ..... *yyyy mm dd*	.....	.....	.....	.....
		.....	.....	.....
..... - ..... - ..... *yyyy mm dd*	.....	.....	.....	.....
		.....	.....	.....

Cell/Gene Therapy Infusion Unit – Manipulation

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 ....

***EX-VIVO* MANIPULATION OF THE PRODUCTS CONTAINED IN THE CELL/GENE THERAPY INFUSION UNIT**

- ☐ No -> Skip MAN PULATION section and go straight to CELL INFUSION PRODUCT FROZEN two pages below
- ☐ Yes -> Continue with MAN PULATION section below
- ☐ Unknown

MANIPULATION AIMS (SKIP THIS SECION IF IT'S A COMMERCIAL PRODUCT)

Recognition of a specific target / antigen

- ☐ No
- ☐ Yes: **TYPE** *(check all that apply)*
  - ☐ Viral ☐ Adenovirus ☐ BK virus ☐ Cytomegalovirus (CMV) ☐ Epstein-Barr virus ☐ Human herpes virus 6 ☐ Human immunodeficiency virus (HIV) ☐ Other virus, specify ……..
  - ☐ Fungal ☐ Candida ☐ Aspergillus ☐ Other fungal, specify ……..
  - ☐ Tumour / cancer antigen(s), specify all……
  - ☐ Other target, specify ……..

MANIPULATION (SKIP THIS SECION IF IT'S A COMMERCIAL PRODUCT)

Processing/Manufacturing Facility

Onsite, by local cell processing facility	☐ No	☐ Yes
Offsite, by a non commercial facility	☐ No	☐ Yes
Offsite, by a commercial facility	☐ No	☐ Yes

Was there a cell selection process?

- ☐ No
- ☐ Yes: Positive ☐ No ☐ Yes
  If Yes, specify cell type……..
  Negative ☐ No ☐ Yes

Expansion

- ☐ No
- ☐ Yes:

Activation

- ☐ No
- ☐ Yes

Induced differentiation

- ☐ No
- ☐ Yes

GENE MANIPULATION

☐ No
☐ Yes: **TYPE**

Gene transfer ☐ No ☐ Yes: ☐ Retroviral vector
☐ Lentiviral vector
☐ Other vector specify .....

Transgene (select all that apply)
☐ CAR, specify all targets .....
☐ TCR, specify all targets ..... / specify HLA element .....
☐ Globin gene, specify……
☐ SCID gene, specify……
☐ Suicide gene, specify.....
☐ Other, specify .....

Gene editing ☐ No ☐ Yes: Manipulated gene ☐ CCR5
☐ Factor IX
☐ Factor VIII
☐ Other gene, specify .....

Other ☐ No ☐ Yes, specify ……

Was the generated cellular product cryopreserved prior to infusion

☐ No
☐ Yes

THERAPY and CELL INFUSION(s)

Chronological number of cell or gene therapy treatment for this patient …....

If number of cell/gene therapy treatment >1:

Same package/product as for the previous cell/gene therapy treatment? ☐ No ☐ Yes ☐ Not applicable

If >1, date of last cell/gene therapy treatment before this one: ..... - .....-.....
yyyy mm dd

If >1, type of last cell/gene therapy treatment before this one: ☐ Allo ☐ Auto

If >1 and Allograft, Was the same donor used for all prior and current cell/gene therapy treatments?

☐ No ☐ Yes

If >1, was last cell/gene therapy treatment performed at another institution?

☐ No ☐ Yes: CIC if known .....

Name of the institution ……

City ……

⇨ If >1, please submit an Annual follow up form before proceeding, **giving the date of the subsequent cell/gene therapy as the date of last contact**. (This is so we can capture relapse data and other events between cell/gene therapies).

Primary aim of the cell/gene therapy treatment *(tick all that apply)*

*IF INDICATION IS THE TREATMENT OF A **PRIMARY DISEASE***

☐ Treatment of Primary diagnosis
☐ Disease relapse or progression
☐ Other, specify ....
☐ Prevention of disease relapse or progression
☐ Refractory disease

Primary aim of the cell/gene 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
☐ Prevention / prophylaxis of GvHD
☐ Treatment of GvHD

Graft function
☐ Unrelated to graft function
☐ Prevention of rejection / promotion of cell engraftment
☐ Graft enhancement
☐ Graft failure treatment

Immune reconstitution
☐ Unrelated to Immune reconstitution
☐ Immune reconstitution

Infections
☐ Unrelated to infections
☐ Prevention / prophylaxis
☐ Treatment

Pathogen involved:
☐ Adenovirus ☐ BK virus ☐ Cytomegalovius (CMV)
☐ Epstein-Barr virus ☐ Human herpex virus
☐ Human immunodeficiency virus (HIV) ☐ Other virus, specify ……..

☐ Candida ☐ Aspergillus ☐ Other fungal, specify ……..

☐ Other, specify ……..

Patient preparative treatment

☐ No ☐ Yes

Specification and dose of the preparative regimen

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/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**
.....		☐ 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 treatment ☐ No ☐ Yes, specify ....

CELL INFUSION EPISODES

Were there more than one cell infusion episode during this treatment or procedure?

☐ No

☐ Yes: Number of cell infusion episodes during this procedure .....

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 name of the Unit as described in the Cell Infusion Unit section

……. ***This item is mandatory if more than one unit was used***

Date of cell infusion episode .....

Reconstitution (infusion) procedure

Where was it done? ☐ Bedside ☐ Pharmacy ☐Cell processing facility
☐ Other, specify…….

Who did it? ……..

Route of infusion *(check all that apply)*

☐ Systemic including Intravenous

☐ Other route .....

Dose of Cells infused *(complete either total number of cells or actual volume infused)*

Number of cells…… Units *(tick one)* ☐ 10^6/kg ☐ 10^6 ☐ 10^8/kg ☐ 10^8
(Not adjusted for cell viability)

Viability…….
or
Actual volume infused…… Units *(tick one)* ☐ ml

TO BE FILLED ONLY FOR **AUTOLOGOUS STEM CELL GENE THERAPY**

CELLS COLLECTED AND INFUSED *(cell type as indicated in the INFUSION UNIT section on page 8)*	Number of cells *(Not adjusted for cell viability)*
Evaluated <u>before</u> manipulation and cryopreservation:	
- Total nb. of nucleated cells	.... - .... x 10^8/kg
- CD 34+	.... - .... x 10^6/kg
Evaluated <u>after</u> manipulation and <u>before</u> cryopreservation:	
- Total nb. of nucleated cells	.... - .... x 10^8/kg
- CD 34+	.... - .... x 10^6/kg
Cells actually infused (after thawing (if thawing) and manipulation (if manipulation))	
- Total nb. of nucleated cells	.... - .... x 10^8/kg
- CD 34+	.... - .... x 10^6/kg

(kg of recipient body weight)*

END OF DAY 0 REGISTRATION

ACUTE LEUKAEMIAS
Primary Acute Myeloid Leukaemia (AML) (1 of 4)
(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

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? ☐ No ☐ Yes:
- ☐ Aplastic anaemia
- ☐ Bloom syndrome
- ☐ Fanconi anaemia
- ☐ Unknown

Donor cell leukaemia?

IF THE PAT ENT 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

ACUTE MYELOID LEUKAEMIA (AML) (2 of 4)

Chromosome analysis at diagnosis (All methods including FISH)

☐ Normal

☐ Abnormal:

Complex karyotype: ☐ No ☐ Yes ☐ Unknown
(3 or more abnormalities)

Monosomal karyotype: ☐ No ☐ Yes ☐ Unknown
(≥ 2 autosomal monosomies or 1 autosomal monosomy + at least 1 structural abnormality)

☐ Not done or failed ☐ Unknown

You can transcribe the complete karyotype: .....

OR

Indicate below those abnormalities that have been **evaluated** and whether they were **Absent** or **Present**

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 only if* 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	☐ Not evaluated
3q26 (EVI1) abnormality type	☐ 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	☐ Not evaluated
t(6;9)	☐ Absent	☐ Present	☐ Not evaluated
abn 5 type *Fill only if above* 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); please specify: _ _ _ _ _	☐ Absent	☐ Present	☐ Not evaluated
abn 7 type *Fill only if* 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); please specify: _ _ _ _ _	☐ 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.....	☐ Absent	☐ Present	

ACUTE MYELOID LEUKAEMIA (AML) (3 of 4)

Molecular Markers at Diagnosis

Molecular marker analysis at diagnosis

☐ Not evaluated ☐ Absent ☐ Present ☐ Unknown

Indicate below those **markers** that have been **evaluated** and whether they were **Absent** or **Present**

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:	☐ 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
Primary Acute Myeloid Leukaemia (AML) (4 of 4)

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	

Status at Cell/Gene therapy

STATUS	NUMBER	TYPE OF REMISSION	
☐ Primary induction failure			
☐ Complete haematological remission (CR)	☐ 1st ☐ 2nd ☐ 3rd or higher	CYTOGENETIC REMISSION ☐ No ☐ Yes ☐ Not evaluated ☐ Not applicable* ☐ Unknown	MOLECULAR REMISSION ☐ No ☐ Yes ☐ Not evaluated ☐ Not applicable* ☐ Unknown
☐ Relapse	☐ 1st ☐ 2nd ☐ 3rd or higher		

* *No abnormalities detected prior to this time point*

ACUTE LEUKAEMIAS
Precursor lymphoid neoplasms *(old ALL)* (main disease code 1)

Disease

Classification:

☐ 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*

☐ T lymphoblastic leukaemia/lymphoma *(old Precursor T-cell ALL)*

CNS involvement ☐ No ☐ Yes

Secondary Origin?

Secondary origin

Related to prior exposure to therapeutic drugs or radiation ☐ No ☐ 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

PRECURSOR LYMPHOID NEOPLASMS (previously ALL)

Chromosome Analysis at Diagnosis

Chromosome analysis at diagnosis (All methods including FISH)

☐ Normal ☐ Abnormal ☐ Not done or failed ☐ Unknown

If abnormal:

Complex karyotype: ☐ No ☐ Yes ☐ Unknown
(3 or more abnormalities)

You can transcr be the complete karyotype: .....

OR

Indicate below which abnormalities have been **evaluated** and whether they were **Absent** or **Present**

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: _ _ _ _ _	☐ 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 number of chromosomes	☐ Absent	☐ Present	☐ Not evaluated
Trisomy: Specify extra chromosome _ _ _ _ _	☐ Absent	☐ Present	☐ Not evaluated
Other hyperdiploid karyotype ..... number of chromosomes	☐ Absent	☐ Present	☐ Not evaluated
Hypodiploidy (<46 chromosomes): *Specify the number of missing chromosomes:*	☐ Absent	☐ Present	☐ Not evaluated
Low hypodiploid, 32-39 chromosomes number of chromosomes	☐ Absent	☐ Present	☐ Not evaluated
Near haploid, 24-31 chromosomes number of chromosomes	☐ Absent	☐ Present	☐ Not evaluated
Monosomy. Specify:	☐ Absent	☐ Present	☐ Not evaluated
Other. number of chromosomes	☐ 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.....	☐ Absent	☐ Present	☐ Not evaluated

PRECURSOR LYMPHOID NEOPLASMS (previously ALL)

Molecular Markers at Diagnosis

Marker analysis
☐ Not evaluated ☐ Absent ☐ Present ☐ Unknown

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
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
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.....	☐ Absent	☐ Present	☐ Not evaluated

White blood cell count at diagnosis (10^9/l): .... - ..... ☐ Not available / unknown

Status at Cell/Gene therapy

STATUS	NUMBER	TYPE OF REMISSION	
☐ Primary induction failure			
☐ Complete haematological remission (CR) ☐ CRi (CR with incomplete haematologic recovery)	☐ 1st ☐ 2nd ☐ 3rd or higher	CYTOGENETIC REMISSION ☐ No ☐ Yes ☐ Not evaluated ☐ Not applicable* ☐ Unknown	MOLECULAR REMISSION ☐ No ☐ 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:

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.....

CNS involvement ☐ No ☐ Yes

Secondary Origin?

Secondary origin

Related to prior exposure to therapeutic drugs or radiation ☐ No ☐ Yes ☐ Unknown

IF THE PAT ENT HAS RECEIVED AN ALLOGRAFT PRIOR TO THE DIAGNOSIS OF ACUTE LEUKAEMIA, ANSWER THE FOLLOW NG QUESTION

Is this a donor cell leukaemia ☐ No ☐ Yes ☐ Not evaluated

Status at Cell/Gene therapy

STATUS	NUMBER	TYPE OF REMISSION	
☐ Primary induction failure			
☐ Complete haematological remission (CR)	☐ 1st ☐ 2nd ☐ 3rd or higher	CYTOGENETIC REMISSION ☐ No ☐ Yes ☐ Not evaluated ☐ Not applicable* ☐ Unknown	MOLECULAR REMISSION ☐ No ☐ 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)*
At least one investigation must be positive

Translocation (9;22)	☐ Absent	☐ Present	☐ Not evaluated
bcr-abl	☐ Absent	☐ Present	☐ Not evaluated

Status at Cell/Gene therapy

PHASE	NUMBER	TYPE OF REMISSION		
☐ Chronic phase (CP)	☐ 1st ☐ 2nd ☐ 3rd or higher	HAEMATOLOGICAL ☐ Yes ☐ No ☐ Not evaluated ☐ Unknown	CYTOGENETIC ☐ Yes ☐ No ☐ Not evaluated ☐ Not applicable* ☐ Unknown	MOLECULAR ☐ Yes ☐ 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:

☐ Chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma

☐ Richter's syndrome

Transformed from a previously known CLL

☐ Yes: Date of original CLL diagnosis .... - .... - ....
yyyy mm dd

☐ No: Primary Richter *(without previous known diagnosis of CLL)*

CYTOGENETICS AT DIAGNOSIS (ALL METHODS INCLUDING FISH)

☐ Not done or failed ☐ Done: Normal ☐ Done: Abnormal ☐ Unknown

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	☐ Absent	☐ Present	☐ Not evaluated

MOLECULAR MARKERS AT DIAGNOSIS

TP53 mutations ☐ Absent ☐ Present ☐ Not evaluated ☐ unknown

Status at Cell/Gene therapy

STATUS	**MINIMAL RESIDUAL DISEASE (MRD)** *(by FACS or PCR)*
☐ 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)
- ☐ PLL, B-cell
- ☐ PLL, T-cell

☐ Hairy Cell Leukaemia

☐ Other leukaemia, specify:_____

PLL ONLY - CYTOGENETICS AT DIAGNOSIS (ALL METHODS INCLUDING FISH)

☐ Not done or failed ☐ Done: Normal ☐ Done: Abnormal ☐ Unknown

inv(14)(q11q32)	☐ Absent	☐ Present	☐ Not evaluated
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	☐ Absent	☐ Present	☐ Not evaluated

T-CELL PLL ONLY - IMMUNOPHENOTYPING of T-cells at diagnosis

NOTE: TdT *(Terminal deoxynucleotidyl transferase)* must be negative

CD4+	☐ No	☐ Yes	☐ Not evaluated
CD8+	☐ No	☐ Yes	☐ Not evaluated

Lymphocyte count ..... 10^9 cells/L

Status at Cell/Gene therapy

STATUS

☐ Complete remission (CR):
☐ Partial remission (PR)
☐ Stable disease (SD)
☐ Relapse *(untreated)*
☐ Progression (PD)
☐ Never treated

LYMPHOMAS
B-Cell and T-cell Non Hodgkin Lymphomas (NHL) (main disease code 3)

Disease

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)
- ☐ Follicular lymphoma
- ☐ Primary cutaneous follicle centre lymphoma
- ☐ Mantle cell lymphoma
- ☐ 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)
- ☐ 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 (Intermediate DLCBL/HD)
- ☐ Other B-cell, specify:_____

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
- ☐ Hepatosplenic T-cell lymphoma
- ☐ Subcutaneous panniculitis-like T-cell lymphoma
- ☐ Mycosis fungoides (MF)
- ☐ 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)
- ☐ Angioimmunoblastic T-cell lymphoma
- ☐ Anaplastic large-cell lymphoma (ALCL), ALK-positive
- ☐ Anaplastic large-cell lymphoma (ALCL), ALK-negative
- ☐ Other T-cell, specify:_____

FOR B-CELL LYMPHOMAS:

Transformed from another type of lymphoma at the event leading to this HSCT

- ☐ No
- ☐ Yes: Date of original diagnosis .... - .... - ....

  yyyy *mm* *dd*

  Indicate the type of the original lymphoma ....

☐ Unknown

Assessments at Diagnosis
Grade and Prognostic scores for specific types of Lymphoma

Waldenström's Macroglobulinemia

International Prognostic Scoring System for Waldenström's Macroglobulinemia (ISSWM)

☐ Low risk (0-1 score points except age >65) ☐ Intermediate risk (score 2 or age >65 alone)
☐ High risk (3-5) ☐ Not evaluated

Follicular lymphoma

Grading

☐ Grade I ☐ Grade II ☐ Grade IIIa ☐ Not evaluated

Prognostic score (FLIPI)

☐ Low risk ☐ Intermediate risk ☐ High risk ☐ Not evaluated

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

All Diffuse large B-cell lymphomas (DLBCL) (see next page for the list)

International Prognostic Index (IPI)

☐ 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

Mycosis fungoides and Sézary syndrome

ISCL/EORTC STAGE

☐ **IA** ☐ **IB** ☐ **IIA** ☐ **IIB** ☐ **IIIA** ☐ **IIIB** ☐ **IVA1** ☐ **IVA2** ☐ **IVB** ☐ **Not evaluated**

Peripheral T-cell lymphoma, Angioimmunoblastic T-cell lymphoma, Anaplastic large-cell lymphomas (ALCL) and Other NOS T- cell lymphomas

International Prognostic Index (IPI)

☐ Low risk (0-1 score points) ☐ Low-Intermediate risk (2) ☐ High-intermediate risk (3)
☐ High risk (4 or 5) ☐ Not evaluated

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)
- Intermediate DLBCL/BL
- Intermediate DLBCL/HD

Chromosome Analysis at any time before HSCT

☐ Normal ☐ Abnormal ☐ Not done or failed ☐ Unknown

If abnormal, please complete this table according to the type of lymphoma diagnosed

	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 HSCT

☐ Not evaluated ☐ Present ☐ Absent ☐ Unknown

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 HSCT

Immunophenotyping tested ☐ Yes ☐ No ☐ Unknown

Provide answers according to the type of lymphoma diagnosed

	Phenotype	Present	Absent	Not evaluated
Mantle cell lymphoma	SOX11	☐	☐	☐
All DLBCL	MYC	☐	☐	☐
	BCL-2/	☐	☐	☐
	BCL-6	☐	☐	☐

Hodgkin Lymphomas

Classification:

- ☐ Nodular lymphocyte predominant
- ☐ Classical predominant
- ☐ Other, specify:_____

Immunodeficiency-associated lymphoproliferative disorders (including PTLD)

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:
    - 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?

☐ No ☐ Yes:

Date of the transplant: ..... (yyy) - ..... (mm) - ..... (dd)

Type of transplant: ☐ Renal ☐ Cardiac ☐ Pulmonary ☐ Other, specify……..

ALL LYMPHOMAS

Status at Cell/Gene therapy

Number of prior lines of treatment ☐ 1 ☐ 2 ☐ 3 or more ☐ None ☐ unknown

Technique used for disease assessment:

CT scan done ☐ No ☐ Yes
PET ☐ Negative ☐ Positive ☐ Not evaluated

STATUS
☐ Never treated
☐ Complete remission (CR)
☐ 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
☐ Disease status unknown

For **Relapse** status:
Histopathological verification of relapse? ☐ No ☐ Yes

Was this patient **refractory** to any line of chemotherapy before this HSCT? ☐ No ☐ Yes

Number of Complete remissions (CR, CRu) achieved by the patient prior to this HSCT: ……..
Count <u>all</u> CR including this one if applicable

Number of Partial remissions (PR) achieved by the patient prior to this HSCT: ……..
Count <u>all</u> PR including this one if applicable

MYELODYSPLASTIC SYNDROME (MDS) (main disease code 6)

Disease

Select only one

WHO Classification at diagnosis:

- ☐ 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

IF THE PAT ENT HAS RECEIVED AN ALLOGRAFT PRIOR TO THE DIAGNOSIS OF ACUTE LEUKAEMIA, ANSWER THE FOLLOW NG QUESTION

Is this a donor cell leukaemia ☐ No ☐ Yes ☐ Not evaluated

CYTOGENETICS DATA

(INCLUDE ALL ANALYSIS BEFORE TREATMENT; DESCRIBE RESULTS OF MOST RECENT COMPLETE ANALYSIS)

Chromosome analysis at diagnosis (All methods including FISH)

☐ Normal

☐ Abnormal:

Complex karyotype: ☐ No ☐ Yes ☐ Unknown
(3 or more abnormalities)

☐ Not done or failed
☐ Unknown

You can transcribe the complete karyotype: .....

OR

Indicate below those abnormalities that have been **evaluated** and whether they were **Absent** or **Present**

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

Marker analysis at diagnosis

☐ Not evaluated ☐ Absent ☐ Present ☐ Unknown

Status at Cell/Gene therapy

Select only one

WHO Classification at time of this treatment:

- ☐ 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	NUMBER
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

☐ 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

CYTOGENETICS AND MOLECULAR MARKERS AT DIAGNOSIS

(INCLUDE ALL ANALYSIS BEFORE TREATMENT; DESCRIBE RESULTS OF MOST RECENT COMPLETE ANALYSIS)

Chromosome analysis (All methods including FISH)
☐ Normal
☐ Abnormal:

Complex karyotype: *(3 or more abnormalities)* ☐ No ☐ Yes ☐ Unknown

☐ Not done or failed ☐ Unknown

You can transcribe the complete karyotype: .....

OR

Indicate below those abnormalities that have been **evaluated** and whether they were **Absent** or **Present**

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

☐ Not evaluated ☐ Absent ☐ Present ☐ Unknown

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

Status at Cell/Gene therapy

WHO Classification at time of treatment:

- ☐ 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	NUMBER
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

- ☐ 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
- ☐ Other, specify:_____

☐ 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

IPSS Risk score for Myelofibrosis

☐ 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 analysis (All methods including FISH)
- ☐ Normal
- ☐ Abnormal

Complex karyotype: ☐ No ☐ Yes ☐ Unknown

☐ Not done or failed ☐ Unknown

You can transcribe the complete karyotype: .....

OR

Indicate below those abnormalities that have been **evaluated** and whether they were **Absent** or **Present**

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

☐ Not evaluated ☐ Absent ☐ Present ☐ Unknown

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 % .....
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	

Status at Cell/Gene therapy

Classification at time of this treatment:

- ☐ 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 ..... - ..... - .....
yyyy mm dd

☐ MPN not otherwise specified

STATUS	NUMBER
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)	

DIPSS Risk score for Myelofibrosis

☐ Low risk ☐ Intermediate-1 ☐ Intermediate-2 ☐ High risk ☐ Not evaluated

PLASMA CELL DISORDERS (PCD) including MULTIPLE MYELOMA (MM) (main disease code 4)

Disease

Classification

- ☐ Multiple myeloma (MM)
  - ☐ MM –heavy chain and light chain *Check light and heavy chain types →*
  - ☐ MM -light chain *Check light chain type only →*
  - ☐ MM -non-secretory

HEAVY CHAIN TYPE
- ☐ IgG
- ☐ IgA
- ☐ IgD
- ☐ IgE
- ☐ IgM *(not Waldenstrom)*

LIGHT CHAIN TYPE
- ☐ Kappa
- ☐ Lambda

- ☐ Plasma cell leukaemia
- ☐ Solitary plasmacytoma of bone
- ☐ Primary amyloidosis
- ☐ POEMS
- ☐ Monoclonal light and heavy chain deposition disease (LCDD/HCDD)
- ☐ Other, specify:_____

STAGE AT DIAGNOSIS
Complete both staging systems

SALMON AND DURIE (MM)

	I	II	III
A	☐	☐	☐
B	☐	☐	☐

ISS

	β2 µglob *(mg/L)*	Albumin *(g/L)*		β2 µglob *(mg/L)*	A bumin *(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)
Not for Primary amyloidosis

☐ Normal

☐ Abnormal:

Complex karyotype: *(3 or more abnormalities)* ☐ No ☐ Yes ☐ Unknown

☐ Not done or failed ☐ Unknown

You can transcribe the complete karyotype: .....

OR

Indicate below those abnormalities that have been **evaluated** and whether they were **Absent** or **Present**

If abnormal, indicate abnormalities found:			
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).....

.....

Molecular analysis
Not for Primary amyloidosis

☐ Absent ☐ Present (at least one) ☐ Not evaluated ☐ Unknown

Status at Cell/Gene therapy

STATUS	NUMBER
☐ 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 including APLASTIC ANAEMIA (BMF) (main disease code 7)

Disease

Classification:

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: _____

Etiology:
- ☐ Secondary to hepatitis
- ☐ Secondary to toxin/other drug
- ☐ Idiopathic
- ☐ Other, 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 11)

Disease

Classification:

- ☐ Thalassaemia: ☐Beta 0 ☐Beta + ☐Beta E ☐Beta S (sickle cell + thalassaemia)
  % 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
- ☐ Head and neck
- ☐ Hepatobiliary
- ☐ Kidney cancer excluding Wilm's tumour
- ☐ Lung cancer, non-small cell
- ☐ Lung cancer, small cell
- ☐ Medulloblastoma
- ☐ Melanoma
- ☐ Other, specify .....
- ☐ 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

	0	1	2	3	4	X	Not evaluated	Unknown
Tumour	☐	☐	☐	☐	☐	☐	☐	☐
Nodes	☐	☐	☐	☐		☐	☐	☐
Metastases*	☐	☐				☐	☐	☐

*For metastases, 0 indicates "No metastasis", 1 indicates "Metastasis" and X indicates "Not evaluable"

Disease-specific staging	I	II	III	IV	Not evaluated	Unknown
	☐	☐	☐	☐	☐	☐

BREAST CARCINOMA ONLY

RECEPTOR STATUS

Estrogen (ER): ☐ Negative ☐ Positive ☐ Not evaluated

Progesterone (PgR): ☐ Negative ☐ Positive ☐ Not evaluated

HER2/neu (c-erb-B2): ☐ Negative ☐ Positive ☐ Not evaluated

HISTOLOGICAL SUBCLASSIFICATION

Axillary lymph nodes at surgery: N° positive / N° 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 TUMOURS ONLY

Histological classification

☐ Seminoma ☐ Non-seminoma

Site of origin

☐ Gonadal

☐ Extragonadal: ☐ retroperitoneal ☐ mediastinal ☐ other sites (specify**) ……..**

Status at Cell/Gene therapy

GERM CELL TUMOURS

Risk category at disease recurrence (or platinum refractoriness) following first line CT

☐ Very Low ☐ Low ☐ Intermediate ☐ High ☐ Very High ☐ Not evaluated

STATUS		
☐ Adjuvant ☐ Never treated (upfront) ☐ Stable disease/no response		
☐Complete remission (CR) ☐ Confirmed ☐ Unconfirmed (CRU*) *CRU – complete response with persistent scan abnormalities of unknown significance	**NUMBER** ☐ 1st ☐ 2nd ☐ 3rd or higher	
☐ 1st Partial response (PR1)		
☐ Relapse	**NUMBER** ☐ 1st ☐ 2nd ☐ 3rd or higher	**SENSITIVITY TO CHEMOTHERAPY** ☐ Sensitive ☐ Resistant ☐ Untreated
☐ Progressive disease (PD)		

Organ(s) involved (*complete only if not in CR***)**

☐ Nodes Below Diaphragm ☐ Nodes Above Diaphragm

☐ Bone ☐ CNS

☐ Lungs ☐ Liver

☐ Soft Tissue

☐ Other: ……

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
- ☐ IPEX syndrome
- ☐ Kostmann syndrome-congenital neutropenia
- ☐ Leukocyte adhesion deficiencies
- ☐ Neutrophil actin deficiency
- ☐ Omenn syndrome
- ☐ PNP deficiency *(Purine nucleoside phosphorylase)*
- ☐ Reticular dysgenesis
- ☐ SCID other, specify: .....
- ☐ SCID, unspecified
- ☐ Wiskott Aldrich syndrome
- ☐ X-linked lymphoproliferative syndrome
- ☐ Other, specify: .....
- ☐ Immune deficiencies, not otherwise specified

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)
- ☐ 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 of metabolism, not otherwise specified

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 (FELH)
- ☐ Langerhans Cell Histiocytosis *(Histiocytosis-X)*
- ☐ Histiocytic sarcoma *(malignant histiocytosis*)
- ☐ Familial erythro/haemophagocytic lymphohistiocytosis
- ☐ Haemophagocytosis (reactive or viral associated)
- ☐ Other, specify:_____

AUTOIMMUNE DISORDERS (main disease code 10)

CONNECTIVE TISSUE

DISEASE

Classification:

☐ Systemic sclerosis (SS)

Involvement/Clinical problem

- ☐ diffuse cutaneous
- ☐ limited cutaneous
- ☐ SSc sine scleroderma
- ☐ Other (MCTD: Mixed Connective Tissue Disease)
- ☐ other, specify:_____

☐ Systemic lupus erythematosus (SLE)

SLEDAI score …….

- ☐ Polymyositis- dermatomyositis
- ☐ Sjögren syndrome
- ☐ Antiphospholipid syndrome
- ☐ Other type of connective tisue disease, specify:_____

VASCULITIS

DISEASE

Classification:

- ☐ Wegener granulomatosis
- ☐ Polyarteritis nodosa
  - ☐ Classical
  - ☐ Microscopic
- ☐ Churg-Strauss
- ☐ Giant cell arteritis
- ☐ Takayasu
- ☐ Behçet's syndrome
- ☐ Overlap necrotising arteritis
- ☐ Other, specify:_____

CIC: ..... Hospital UPN: ..... Date of the first cell/gene therapy infusion..... .... - .... - .....

(Do not write here the date of any HSCT) *yyyy* *mm* *dd*

AUTOIMMUNE DISORDERS (main disease code 10)

ARTHRITIS

DISEASE

Classification:

☐ Rheumatoid arthritis
☐ Psoriatic arthritis/psoriasis
☐ Juvenile idiopathic arthritis (JIA), systemic (Stills disease)
☐ Juvenile idiopathic arthritis (JIA), articular: Onset ☐ Oligoarticular ☐ Polyarticular
☐ Juvenile idiopathic arthritis: other, specify:_____
☐ Other arthritis: .....

NEUROLOGICAL

DISEASE

Classification:

☐ **MULTIPLE SCLEROSIS**

Disease status ☐ primary progressive
☐ secondary progressive
☐ relapsing/remitting
☐ other:_____

☐ Myasthenia gravis
☐ Amyotrophic lateral sclerosis (ALS)
☐ Chronic inflammatory demyelinating polyneuropathy (CIDP)
☐ Other autoimmune neurological disorder, specify:_____

HAEMATOLOGICAL

DISEASE

Classification:

☐ Idiopathic thrombocytopenic purpura (ITP)
☐ Haemolytic anaemia
☐ Evan syndrome
☐ Autoimmune lymphoproliferative syndrome (primary diagnosis, not subsequent to transplant)
☐ Other haematological autoimmune disease, specify:_____

AUTOIMMUNE DISORDERS (main disease code 10)

BOWEL

DISEASE

Classification:
☐ Crohn's disease
☐ Ulcerative colitis
☐ Other autoimmune bowel disease, specify:_____

OTHER AUTOIMMUNE DISORDER

DISEASE

Classification:
☐ Graves' disease
☐ Diabetes type 1
☐ Other autoimmune, specify:_____

OTHER PRIMARY DISEASE

NEUROLOGIC DISORDES (main disease code 12)

Classification:

- ☐ Duchenne Muscular Distrophy
- ☐ Acute cerebral vascular ischemia
- ☐ ALS, amiotrophic lateral sclerosis
- ☐ Parkinson disease
- ☐ Spinal cord injury
- ☐ Cerebral palsy
- ☐ Congenital hydrocephalus
- ☐ Other, specify:_____

CARDIOVASCULAR DISEASE (main disease code 13)

Classification:

- ☐ AMI, acute myocardial infarction
- ☐ Chronic coronary artery disease (ischemic, cardiomyopathy)
- ☐ Heart failure (non-ischemic etiology)
- ☐ Other cardiovascular disease
- ☐ Limb ischemia
- ☐ Thromboangitis obliterans
- ☐ Other peripheral vascular disease
- ☐ Other, specify:_____

MUSCULOSKELETAL (main disease code 15)

Classification:

- ☐ Avascular necrosis of femoral head
- ☐ Osteoarthritis
- ☐ Osteogenesis imperfecta
- ☐ Traumatic joint injury
- ☐ Other, specify:_____

Cellular and Gene Therapy Form

Status at Last Assessment
(at Day 100, 6 months, Annual Follow Up)

CENTRE IDENTIFICATION

EBMT Code (CIC): .... Hospital: ..... Unit: .....

Contact person.....

PATIENT DATA

Date of this Report: ..... - ..... - .....
yyyy *mm* *dd*

EBMT Registry Unique Identification Code (UIC) .....

Hospital Unique <u>Patient</u> Number or Code (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 <u>not</u> to the treatment.*

Other type of patient identification codes (AIEOP etc.): ……
(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))

Date of Birth: ..... - ..... - .....
yyyy *mm* dd

INDICATE THE PERIOD COVERED BY THIS REPORT

☐ **Day 100** ☐ **6 months** ☐ **Annual Follow Up**

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 Cell/Gene therapy + set period (as indicated above – 100 Days, 6 months, annual) approximately.

Last assessment for this report: ..... - ..... - ..... ☐ Not applicable
yyyy *mm* *dd*

Date of death: ..... - ..... - ..... ☐ Not applicable
yyyy *mm* *dd*

RECOVERY **Complete ONLY for DAY 100**

COMPLETE ONLY FOR AUTOLOGOUS STEM CELL GENE THERAPY

Absolute neutrophil count (ANC) recovery *(Neutrophils ≥0.5X10⁹ /L)*

☐ No: Date of last assessment: ..... - ..... - .....
yyyy *mm* *dd*

☐ Yes: Date of ANC recovery: ..... - ..... - ..... *(first of 3 consecutive values after 7 days without transfusion)*
yyyy *mm* *dd*

☐ Never below
☐ Unknown

Platelet reconstitution

Platelets **≥20** x 10^9/l; *(first of 3 consecutive values after 7 days without transfusion)*

☐ No
☐ Yes: Date Platelets ≥ 20 x 10^9/l ..... - ..... - .....
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 transfusion)*

☐ No
☐ Yes: Date Platelets ≥ 50 x 10^9/l ..... - ..... - .....
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
yyyy *mm* *dd*

Early graft loss *(Engraftment followed by loss of graft within the first 100 days)*

☐ No ☐ Unknown
☐ Yes: date of graft failure .... - .... - ....
yyyy *mm* *dd*

TREATMENT FOR AN EARLY GRAFT FAILURE
(If engraftment failure)

☐ No
☐ Growth factors
☐ **Subsequent** transplant *(please complete a new transplant form)*:
Date: .... - .... - .... ☐ subsequent AUTOgraft *(must have prior conditioning)*
yyyy *mm* *dd* ☐ subsequent ALLOgraft
☐ Autologous PBSC **re-infusion/boost** *(no preparative treatment or conditioning)*
☐ Autologous BM **re-infusion/boost** *(no preparative treatment or conditioning)*
☐ Other: .....

CIC: ..... Hospital UPN: ..... Date of the first cell/gene therapy infusion..... .... - .... - .....
(Do not write here the date of any HSCT) *yyyy* *mm* *dd*

Graft assessment

Complete ONLY for MONTH 6 and ANNUAL FOLLOW UP

FOR PATIENTS THAT HAVE RECEIVED GENETICALLY MODIFIED AUTOLOGOUS STEM CELL/GENE THERAPY OR FOR PATIENTS THAT HAVE RECEIVED AN HSCT PRIOR TO THIS CELL/GENE THERAPY TREATMENT

Graft loss

☐ No ☐ Yes: Date of graft failure ..... - ..... - ..... ☐ Not evaluated
yyyy *mm* *dd*

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 cell/gene therapy treatment

☐ 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: ..... - ..... - ....
yyyy *mm* *dd*

(LYMPHOMA only) For **Relapse** status:
Histopathological verification of relapse? ☐ No ☐ Yes

TO BE ANSWERED ONLY WHEN THE INDICATION WAS THE TREATMENT OF COMPLICATIONS DERIVED FROM A PREVIOUS TRANSPLANT

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: ..... - ..... - ....
yyyy *mm* *dd*

Current Haematological findings

Hb (g/dL) ..... ☐ Not evaluated
Platelets (10^9/L) ..... ☐ Not evaluated
Were platelets transfused within 7 days before date of the test? ☐ No ☐ Yes

White Blood Cells (10^9/L) ..... ☐ Not evaluated
% neutrophils ..... ☐ Not evaluated
% Lymphocytes ..... ☐ Not evaluated
% haematocrit ..... ☐ Not evaluated
Was RBC transfused within 30 days before date of the test? ☐ No ☐ Yes

Complications since the last report

DO NOT INCLUDE INFORMATION ON COMPLICATIONS THAT WERE RESOLVED BEFORE THE CELL/GENE THERAPY THIS FORM REFERS TO AND THOSE THAT WERE REPORTED PREVIOUSLY AND WERE RESOLVEDSINCE

Did GvHD occur? ☐ No (skip rest of this box) ☐ Yes:

Onset date: ..... - ..... - .....
yyyy *mm* *dd*

Acute GvHD

Maximum Grade:

☐ 0 (none) ☐ I ☐ II ☐ III ☐ IV
☐ Present but grade unknown ☐ Not evaluated

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 Therapy ☐ No ☐ Yes
Resolved? ☐ No ☐ Yes

Chronic GvHD

Maximum extent <u>during this period</u>

☐ Limited ☐ Extensive ☐ Unknown

Maximum NIH score <u>during this period</u>

☐ Mild ☐ Moderate ☐ Severe ☐ Not calculated

Resolved? ☐ No ☐ Yes

Was the patient transferred to the Intensive Care Unit? ☐ No ☐ Yes

Was inpatient admission and care needed (not ICU)? ☐ No ☐ Yes

Was B-Cell Aplasia present in this last period ☐ No *(skip to the next page)* ☐ Yes: % of B-Cells …..

If there was no B-Cell Aplasia present at the time of this Cellular Therapy, please answer the following:

Date of onset: ..... - ..... - ..... Resolved? ☐ No ☐ Yes: date: ..... - ..... - .....
yyyy *mm* *dd* *yyyy* *mm* *dd*

Other complications or toxicities during this period

☐ No -> Skip TOXICIT ES table below and go straight to INFECTIOUS COMPLICATIONS on page 56
☐ Yes -> Continue with the TOXICITIES below
☐ Unknown

TOXICITIES/COMPLICATIONS

Cytokine release syndrome (CRS) (Macrophage Activation Syndrome (MAS))

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

Scale/criteria was used to determine the Grade of CRS…….

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

Resolved? ☐ No ☐ Yes

Neurotoxicity

☐ No ☐ Yes: Select and complete all that apply

☐ Altered mental status

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

Resolved? ☐ No ☐ Yes

☐ Aphasia

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

Resolved? ☐ No ☐ Yes

☐ Hemiparesis or other focal motor deficit

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

Resolved? ☐ No ☐ Yes

☐ Seizure(s)

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

Resolved? ☐ No ☐ Yes

☐ Tremors

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

Resolved? ☐ No ☐ Yes

☐ Visual hallucinations

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

Resolved? ☐ No ☐ Yes

☐ Encephalopathy

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

Resolved? ☐ No ☐ Yes

☐ Cerebral Oedema

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

Resolved? ☐ No ☐ Yes

☐ Other, specify ……

Onset date: ..... - ..... - ..... Grade *(if applicable)*:……
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

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 60*

Resolved? ☐ No ☐ Yes

☐ Liver

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

Resolved? ☐ No ☐ Yes

☐ Lungs

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

Resolved? ☐ No ☐ Yes

☐ Heart

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

Resolved? ☐ No ☐ Yes

☐ Kidney

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

Resolved? ☐ No ☐ Yes

☐ Gastrointestinal

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

Resolved? ☐ No ☐ Yes

☐ Other organ, specify……

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

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 60*

Resolved? ☐ No ☐ Yes

Hemorrhagic stroke

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

Resolved? ☐ No ☐ Yes

Bone marrow aplasia/failure

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Specify……
yyyy *mm* *dd*

Grade:……

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

Resolved? ☐ No ☐ Yes

Hypogammaglobulinemia

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

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 60*

Resolved? ☐ No ☐ Yes

Insertional mutagenesis

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Grade:……
yyyy *mm* *dd*

Exacerbation of existing neurological disorder

☐ No ☐ Yes:

Onset date: .... - .... - .... Specify………………………………………………
yyyy mm dd

Grade:………

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60*

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 60*

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 60*

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 60*

Resolved? ☐ No ☐ Yes

INFECTIOUS COMPLICATIONS WITHIN THIS REPORTING PERIOD

INFECTION RELATED COMPLICATIONS

☐ No -> Skip INFECTIOUS COMPLICATIONS below and go straight to SECONDARY MALIGNANCY on page 56
☐ Yes -> Continue with the INFECTIONS below

Bacteremia (report all episodes)

☐ No ☐ Yes (report all episodes):
(In case of the same pathogen, report episodes occuring after 14 days)

1) Onset date: ..... - ..... - ..... Pathogen: .....
yyyy mm dd
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

2) Onset date: ..... - ..... - ..... Pathogen: .....
yyyy mm dd
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

3) Onset date: ..... - ..... - ..... Pathogen: .....
yyyy mm dd
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

4) Onset date: ..... - ..... - ..... Pathogen: .....
yyyy mm dd
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

5) Onset date: ..... - ..... - ..... Pathogen: .....
yyyy mm dd
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

Invasive fungal disease, including candidemia

☐ No ☐ Yes (report all episodes):

1) Onset date: ..... - ..... - ..... Pathogen: ..... Infection site: ☐ Lung ☐ Blood ☐ CNS ☐ Other:.....
yyyy mm dd
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

2) Onset date: ..... - ..... - ..... Pathogen: ..... Infection site: ☐ Lung ☐ Blood ☐ CNS ☐ Other:.....
yyyy mm dd
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

3) Onset date: ..... - ..... - ..... Pathogen: ..... Infection site: ☐ Lung ☐ Blood ☐ CNS ☐ Other:.....
yyyy mm dd
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

4) Onset date: ..... - ..... - ..... Pathogen: ..... Infection site: ☐ Lung ☐ Blood ☐ CNS ☐ Other:.....
yyyy mm dd
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

5) Onset date: ..... - ..... - ..... Pathogen: ..... Infection site: ☐ Lung ☐ Blood ☐ CNS ☐ Other:.....
yyyy mm dd
Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

CNS infection

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

Pneumonia

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

C. difficile infection

☐ No ☐ Yes:

Onset date: ..... - ..... - .....
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* 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 60* Resolved? ☐ No ☐ Yes

Hepatitis

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

Retinitis

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

Cystitis

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

Skin infection

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

Upper respiratory tract infection

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

CMV reactivation

(DNA-emia in serum/plasma/blood)

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Highest value date: ..... - ..... - ..... Highest value: ……cp/ml
yyyy *mm* *dd* *yyyy* *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

EBV reactivation

(DNA-emia in serum/plasma/blood/PMN)

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Highest value date: ..... - ..... - ..... Highest value: ……cp/ml
yyyy *mm* *dd* *yyyy* *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

HHV6 reactivation

(DNA-emia in serum/plasma)

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Highest value date: ..... - ..... - ..... Highest value: ……cp/ml
yyyy *mm* *dd* *yyyy* *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

Adenovirus reactivation

(DNA-emia in serum/plasma)

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Highest value date: ..... - ..... - ..... Highest value: ……cp/ml
yyyy *mm* *dd* *yyyy* *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

Other virus reactivation

(DNA-emia in serum/plasma)

☐ No ☐ Yes: specify…….

Onset date: ..... - ..... - ..... Highest value date: ..... - ..... - ..... Highest value: ……cp/ml
yyyy *mm* *dd* *yyyy* *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

Other Infectious Complications

☐ No ☐ Yes:

Onset date: ..... - ..... - ..... Pathogen: ……..
yyyy *mm* *dd*

Treated: ☐ No ☐ Yes: *add details to Treatment for Complications on page 60* Resolved? ☐ No ☐ Yes

Did a secondary malignancy occur?

☐ No ☐ Yes:

Date of diagnosis: ..... - ..... - .....
yyyy *mm* *dd*

Diagnosis: .....

Histologic Type:……..

Location:……..

Was sample/biopsy obtained ☐ No ☐ Yes

Is this secondary maligancy derived from cells that composed or were part of the infused medicinal product or cell/gene therapy product ?
(not applicable if the Cell Infusion Unit is a commercial product)

☐ No ☐ Yes ☐ Not applicable

Did autoimmune disorder occur? ☐ No ☐ Yes, specify ……

Date of diagnosis ..... - ..... - .....
yyyy *mm* *dd*

POST-THERAPY TREATMENT

Additional Disease/Side Effects Treatment

Please include only systemic treatments

Complete ONLY for DAY 100 and MONTH 6 assessments

Did the patient undergo additional treatment during or immediately after the cell/gene therapy?

- ☐ No (continue to First Relapse/Progression, page 62)
- ☐ Yes, indicate below

Combined /concomitant therapies planned before this Cell/Gene Therapy treatment to optimize efficency

☐ No ☐ Yes, specify in the table below

Was this treatment given:

- ☐ Simultaneously to the cell/gene therapy
- ☐ After the cell/gene therapy episode was finished
- ☐ Unknown

Drug/Regimen (specify)	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

Other type of treatment ☐ No ☐ Yes, specify ..... ☐ Unknown

Complete ONLY for ANNUAL FOLLOW UP

Is patient getting any medications?

- ☐ No (skip to page 62)
- ☐ Yes

If yes, are those treatments in relation to the Cell/Gene Therapy or its indication?

- ☐ No (skip to First Relapse/Progression, page 62)
- ☐ Yes, specify below.

Unplanned treatment for complications

☐ No ☐ Yes, specify in the table below

Drug/Regimen (specify)	Indication (as specified in the Complications section on pages 51 to 56)	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 Cell/Gene Therapy failure

☐ No ☐ Yes, specify in the table below

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

☐ No ☐ Yes, specify ………………………………….. ☐ Unknown

First Relapse/Progression or Significant worsening after Cell/Gene 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)

☐ No

☐ Yes: Date first seen ..... - ..... - .....
yyyy *mm* *dd*

☐ Continuous progression since cell/gene therapy

HAEMOGLOBINOPATHY ONLY

☐ No transfusion required
☐ Transfusions required: Date of the 1st transfusion ..... - ..... - .....
yyyy *mm* *dd*

Quality of Life

Complete ONLY for ANNUAL FOLLOW UP

PREGNANCY AFTER CELL/GENE THERAPY

Has patient or partner become pregnant after this Therapy?

☐ No ☐ Yes: Did the pregnancy result in a live birth?

- ☐ No:
  - ☐ Abortion (elective, therapeutic, spontaneous)
  - ☐ Stillbirth
- ☐ Yes:
  - ☐ Healthy
  - ☐ Affected by a disease, specify……..
  - ☐ Full-term
  - ☐ Premature
- ☐ Unknown

☐ Unknown

Survival Status

☐ Alive ☐ Dead ☐ Check here if patient lost to follow up

If alive: Performance score of the patient at the last assessment
SYSTEM USED *(choose only one)*:

☐ Karnofsky or ☐ Lansky: Score: ☐ 10 ☐ 20 ☐ 30 ☐ 40 ☐ 50 ☐ 60 ☐ 70 ☐ 80 ☐ 90 ☐ 100

☐ ECOG: Score: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

If dead: Main Cause of Death *(check only one main cause)*:

☐ Relapse or Progression/Persistent disease
☐ Cell/Gene Therapy related: .....
☐ HSCT Related Cause
☐ Unknown
☐ Other: .....

Contributory Cause of Death *(check as many as appropriate)*:

☐ 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:.....

Persistence of the Infused Cells

(COMPLETE ONLY FOR NON-COMMERCIAL PRODUCTS)

Were tests performed to detect the persistence of the cellular products during this period?

☐ No ☐ Yes: Date of the last test ..... - ..... - .....
yyyy *mm* *dd*

Source of cells used for the test: ☐ Bone Marrow ☐ Peripheral Blood ☐Other, specify……..

Technique used /

☐ Molecular (PCR) ☐ Flow cytometry ☐ Chimaerism ☐ Imaging ☐ Immunohistochemistry

☐ Other, specify ……..……..

Were cells detected?

☐ No

☐ Yes: For Stem Cell Gene Therapy - percent of cells carrying the transgene ……..%