Title	Non-interventional, post-authorization safety study (PASS) of patients treated with commercially available liso-cel (lisocabtagene maraleucel) for large B-cell lymphomas
Protocol Version Identifier	JCAR017-BCM-005 (also known as CA082-P21)
Date of Last Version of Protocol	08-Apr-2025
Date of Protocol Version	22-Dec-2025
EU PAS Register Number	EUPAS103855
Active Substance	lisocabtagene maraleucel (liso-cel, JCAR017/BMS-986387)
Medicinal Product	BREYANZI®
Product Reference	EU/1/22/1631/001
Procedure Number	EMEA/H/C/004731/0000
Marketing Authorization Holder(s)	Bristol-Myers Squibb Pharma EEIG
Joint PASS	No
Research Question and Objectives	Primary Objectives • To characterize the incidence of selected adverse drug reactions (ADRs), as outlined in the Summary of Product Characteristics (SmPC), in patients treated with liso-cel in the postmarketing setting. • To characterize the severity of the selected ADRs. • To monitor for potential clinically important adverse events (AEs) that have not yet been identified as part of the liso-cel safety profile. Secondary Objectives • To assess long-term effectiveness in patients treated with liso-cel in the postmarketing setting in NHL histologies (LBCL, FL, MCL). • To assess the liso-cel safety and effectiveness profile in certain subgroups including but not limited to: – large B-cell lymphoma subtypes (eg, diffuse large B-cell lymphoma [DLBCL] not otherwise specified [NOS], high grade B-cell lymphoma [HGBCL], primary mediastinal B-cell lymphoma [PMBCL], follicular lymphoma Grade 3B [FL3B]) – NHL histology (LBCL, FL, MCL) – number of prior lines of systemic therapy – geographical regions (eg, Europe) – subjects aged ≥ 75 years – subjects with comorbid conditions (eg, renal impairment, reduced cardiac function) – subjects with secondary central nervous system (CNS) involvement – subjects with Eastern Cooperative Oncology Group (ECOG) performance score ≥ 2 – possible prognostic factors (eg, high-risk international prognostic index [IPI])

	– subjects previously exposed to anti-CD19 therapy – subjects with low pre-leukapheresis absolute lymphocyte count (ALC) (< 0.3×10^9/L) – subjects treated with out-of-specification (OOS) product Exploratory Objective • To characterize the association between liso-cel effectiveness and CD19 expression obtained prior to liso-cel infusion.
Country(-ies) of Study	United States (US); European countries; other countries may be included
Author	
MAH Contact Person	

SIGNATURE PAGE

Approval is archived in an electronic management system

Signature of Study Director

Printed Name of Study Director

Date Signed _____

Approval is archived in an electronic management system

Signature of Qualified Person Responsible for Pharmacovigilance

Printed Name of Qualified Person Responsible for Pharmacovigilance

Date Signed _____

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
ALC	absolute lymphocyte count
ALL	acute lymphoblastic leukemia
ANC	absolute neutrophil count
ASCT	autologous hematopoietic stem cell transplantation
BCL	B-cell lymphoma
BMS	Bristol-Myers Squibb Company
BTK	Bruton's tyrosine kinase
CAR	chimeric antigen receptor
CAR T cell	chimeric antigen receptor T cell
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete response
CRF	case report form
CRID	CIBMTR Research Identification
CRR	complete response rate
CRS	cytokine release syndrome
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
Cytogen.	cytogenetic
DCCPS	Division of Cancer Control and Population Sciences
DLBCL	diffuse large B-cell lymphoma
DoR	duration of response
EBMT	European Society for Blood and Marrow Transplantation
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EGFRt	truncated human epidermal growth factor receptor
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS Register	European Union electronic Register of Post-Authorisation Studies

Abbreviation	Definition
EURD	European Union Reference Dates
EZH2	Enhancer of Zeste Homolog 2
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FL	follicular lymphoma
FL3B	follicular lymphoma Grade 3B
FN3	FormsNet3
GCB	germinal center B-cell-like
GEP	gene expression profiling
GVHD	graft-versus-host disease
HCP	healthcare professional
HCT	hematopoietic cell transplantation
HGBCL	high-grade B-cell lymphoma
ICF	informed consent form
ID	identifier
IPI	International Prognostic Index
IS	infused set
IV	intravenously
KM	Kaplan-Meier
MAH	Marketing Authorization Holder
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MHA	Master Healthcare Data Agreement
NHL	non-Hodgkin lymphoma
NCI	National Cancer Institute
NK	natural killer
NOS	not otherwise specified
ORR	overall response rate
OOS	out of specification
OS	overall survival
PASS	postauthorization safety study
PET	positron emission tomography
PFS	progression-free survival
PI3K	phosphoinositide 3-kinase
PMBCL	primary mediastinal large B-cell lymphoma
PR	partial response

Abbreviation	Definition
PSUR	periodic safety update report
PSUSA	periodic safety update report single assessment
PT	Preferred Term
QPPV	Qualified Person for Pharmacovigilance
R-CHOP	rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone
R/R	relapsed/refractory
Resp. Ass.	respiratory assessment
SAP	statistical analysis plan
scFv	single chain variable fragment
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TBC	to be confirmed
TLS	tumor lysis syndrome
TTNT	time to next treatment
US	United States
WHO	World Health Organization

3 RESPONSIBLE PARTIES

This noninterventional registry-based category 1 post-authorization safety study (PASS) is conducted by Bristol-Myers Squibb Company (BMS) and represents a condition of the European Medicines Agency (EMA) marketing authorization application (MAA) for liso-cel in its approved indications.

The main responsible parties are listed in Table 3-1.

Table 3-1: Responsible Parties

MAH:	Bristol-Myers Squibb Pharma EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867 Ireland
Main Author:	
Study Director:	
Principal Investigator:	Not applicable
EU QPPV:	

EU, European Union; QPPV, Qualified Person for Pharmacovigilance.

4 ABSTRACT

Title: Non-interventional, post-authorization safety study (PASS) of patients treated with commercially available liso-cel (lisocabtagene maraleucel) for large B-cell lymphomas

Rationale and Background:

The purpose of this study is to further characterize the safety profile of liso-cel in the postmarketing setting.

This PASS will include patients from existing independent registries, such as, but not limited to, the European Society for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR).

This study will be conducted in line with the Appendix 1 (Proposed Data Elements Relating to Efficacy and Safety) of the European Medicines Agency (EMA) 15-May-2018 report on chimeric antigen receptor (CAR) T cell therapy registries workshop.

Liso-cel is a genetically modified autologous cell-based product consisting of purified CD8+ and CD4+ T cells, in a defined composition, expressing CARs targeting CD19 as tumor-associated antigen.

Potential short- and long-term safety findings associated with the treatment of B-cell malignancies with liso-cel include, but are not limited to, cytokine release syndrome (CRS), neurotoxicities, cytopenias, infections, and secondary malignancies.

Objectives:

Primary objectives

- To characterize the incidence of selected adverse drug reactions (ADRs), as outlined in the Summary of Product Characteristics (SmPC), in patients treated with liso-cel in the postmarketing setting.
- To characterize the severity of the selected ADRs
- To monitor for potential clinically important adverse events (AEs) that have not yet been identified as part of the liso-cel safety profile.

Secondary objectives

- To assess long-term effectiveness in patients treated with liso-cel in the postmarketing setting.
- To assess the liso-cel safety and effectiveness profile in certain subgroups including but not limited to:
  - large B-cell lymphoma subtypes (eg, diffuse large B-cell lymphoma [DLBCL] not otherwise specified [NOS], high grade B-cell lymphoma [HGBCL], primary mediastinal B-cell lymphoma [PMBCL], follicular lymphoma Grade 3B [FL3B]
  - NHL histology (LBCL, FL, MCL)
  - number of prior lines of systemic therapy
  - geographical regions (eg, Europe)
  - subjects aged ≥ 75 years
  - subjects with comorbid conditions (eg, renal impairment, reduced cardiac function)
  - subjects with secondary central nervous system (CNS) involvement
  - subjects with Eastern Cooperative Oncology Group (ECOG) performance score ≥ 2
  - possible prognostic factors (eg, high-risk international prognostic index [IPI])
  - subjects previously exposed to anti-CD19 therapy
  - subjects with low pre-leukapheresis absolute lymphocyte count (ALC) ($< 0.3 \times 10^9$/L)
  - subjects treated with out-of-specification (OOS) product

Exploratory Objective

- To characterize the association between liso-cel effectiveness and CD19 expression obtained prior to liso-cel infusion.

Study Design:

This study is designed as a noninterventional cohort study that is based on secondary use of data from existing independent registries of patients with lymphomas treated with liso-cel therapy in the postmarketing setting, which includes patients treated with OOS product.

Data from at least 750 patients with a target of 1000 patients – of which a minimum of 200 patients will come from the European countries – will be collected until death or withdrawal of consent or up to 15 years, whichever occurs first.

This PASS is expected to require up to 5 years to select the planned number of patients globally.

This study is a single-cohort study with no comparator treatment. Hence, its design does not involve any hypothesis testing regarding a potential difference (in safety or effectiveness) between treatment groups.

Study Endpoints

Primary Safety Endpoint(s)

Incidence and severity of selected ADRs reported post liso-cel infusion:

- Secondary malignancies
- Cytokine release syndrome (CRS) all grades
- Neurotoxicities all grades
- Prolonged cytopenias
- Pregnancy outcome
- Other AEs considered related to liso-cel treatment (Grade ≥ 3, where applicable)

Secondary Effectiveness Endpoint(s)

- Overall response rate (ORR)
- Complete response rate (CRR)
- Duration of response (DoR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Time to next treatment (TTNT)

Exploratory Endpoint(s)

- CD19 expression in tumor biopsies prior to liso-cel infusion

Eligibility Criteria

All patients who meet the following inclusion criterion will be selected from the registries:

- Patient must have been treated with at least 1 infusion of liso-cel in the postmarketing setting for an approved indication according to the EMA SmPC, including large B-cell lymphomas (DLBCL, HGBCL, PMBCL, and FL3B), FL and MCL indications. Patients treated with OOS product will also be eligible.

Patients who meet the following exclusion criterion will not be eligible for selection from the registries:

- Patients known to be participating in investigational studies at the time of liso-cel infusion.

Analysis Set:

Due to the noninterventional nature of the study, commonly used analysis sets like the intent to treat set or the per protocol set are not defined in this study.

- The **Infused Set (IS)** is defined as all patients selected from the registry and meeting the study eligibility criteria, where baseline and disease classification information is available.

- The **Safety and Effectiveness Set (SES)** is defined as all patients from the IS with postinfusion safety or effectiveness information.

Data to be Collected:

The following information will be collected from the registries and from internal sources:

- General identifiers (eg, patient code, treatment center identifier)
- Liso-cel product attributes
- Key processes related to liso-cel treatment and associated dates (eg, leukapheresis, liso-cel manufacturing, lymphodepleting therapy, liso-cel infusion, follow-up assessments)
- Demographics (among other possible data, patient's age, sex, height, weight, country, region)
- Baseline characteristics including primary disease (eg, non-Hodgkin lymphoma [NHL]) and disease subtype (eg, NHL histology), prior therapy lines, disease status (eg, relapsed or refractory), prognostic information (eg, international prognostic index [IPI] score), performance score (ECOG or Karnofsky), extranodal involvement (including CNS involvement), comorbidity and organ impairment (eg, renal impairment, reduced cardiac function), CD19 expression data when available
- Safety information post-liso-cel treatment including secondary malignancies, liso-cel-related AEs (eg, neurotoxicity, CRS, prolonged cytopenias), pregnancy outcome, concomitant medications
- Effectiveness assessments and survival status post-liso-cel treatment

Study Size Justification:

Since this is a single-arm noninterventional cohort study with no comparisons and no statistical hypothesis testing, no formal powered sample size calculation is possible. Instead, a fixed number of at least 750 patients from registries is used based on pragmatic nonstatistical reasons, which is considered feasible within the estimated 5-year selection period. The study sample size is supported from a statistical point of view by providing precision estimates (see below).

Precision estimates, based on incidences taken from the literature, are provided by calculating exact 95% Clopper Pearson confidence intervals (CIs; based on a binomial distribution) (see table below).

Assumed incidences for secondary malignancies were taken from reported incidences of an advanced DLBCL population in Surveillance, Epidemiology, and End Results (SEER) 18 regions comprising a total of 25,452 patients.[1]

Thus, in conclusion, if similar incidences to the SEER and Abramson, 2020 are observed in the JCAR017-BCM-005 study, a sample size of at least 750 subjects would provide sufficient precision for a meaningful interpretation of the observed incidences.

Data Source	Description	No. of Patients	Observed Incidence	Incidence Proportion	Clopper Pearson 95% CI lower [for 750 patients]	Clopper Pearson 95% CI upper [for 750 patients]
SEER 18 Regions, 2018[1]	Incidence of non-Hodgkin lymphoma	25,452	246	0.010	0.004	0.019
	Incidences of secondary malignancies at all sites	25,452	1,950	0.077	0.058	0.097

DCCPS, Division of Cancer Control and Population Sciences; No., number.

Source: SEER Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 18 Regs/National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission.[1]

Data Analysis: In this noninterventional cohort study, results will be analyzed and reported descriptively; no formal hypothesis testing is planned.

Confidence intervals will be presented as 2-sided 95% intervals unless specified differently for specific analyses.

Summary statistics will consist of the number and percentage of patients in each category for discrete variables, whereas for continuous variables the sample size, mean, median, standard deviation, minimum, and maximum will be given.

A detailed statistical analysis plan (SAP) will be finalized before the first analysis.

Milestones:

- Date of Initial Registry-based study Protocol Submission to EMA as part of Marketing Authorization Application: 29-Jun-2020
- Date of Final Registry-based study Protocol Approval from EMA: 01-Dec-2022[a]
- Start of data collection:[b] 17-Mar-2023[a]
- Registration in the European Union electronic Register of Post-Authorization Studies (EU PAS Register): 17-Mar-2023
- Study Progress Updates: Per the Periodic safety update report (PSUR) cycle according to the EU reference dates (EURD) list
- Interim reports:[c] At year 5, 10, and 15 or when last patient is out of the registry-based study
- Date of Study Completion:[d] Q4 2042
- Date of Final Study Report Submission to EMA: Q4 2043

[a] Depending on the European Commission (EC) decision and protocol approval timeline.

[b] As the data collection in the EBMT Registry is independent of this study (secondary use of data), the start of data collection corresponds to the date from which data extraction starts. First data extraction for Study JCAR017-BCM-005 will take place 3 months after protocol approval from EMA.

[c] Interim reports will be prepared at Year 5, Year 10, and Year 15 after EC decision date or when the last patient is out of the registry-based study.

[d] Fifteen years after reaching the defined patient number, no further data will be included in the study analyses.

5 AMENDMENTS AND UPDATES

Table 5-1: Information on Protocol Amendments

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	30-May-2023	1-9	• Title, eligibility criteria, and other details in the abstract updated to reflect the inclusion of an extended large B-cell lymphoma indication Background information updated to reflect therapeutic context for all diseases/indications covered in the extended label, including large B-cell lymphoma patients with rarer histologies; to reflect evolutions in the treatment landscape and to reflect available therapies in the second-line setting; and to include additional clinical trial data obtained in patients treated with liso-cel as secondline therapy • Additional exploratory objective related to CD19 expression added • Other minor revisions made eg, administrative changes, corrections and clarifications throughout the protocol	The reason for this amendment is to support an extension of the EMA-approved indication of Breyanzi to include treatment of adult patients in second-line (2L) large B-cell lymphoma. As a consequence, the JCAR017-BCM-005 protocol was amended to broaden eligibility to the 2L large B-cell lymphoma indication and expand the collection of safety and effectiveness data to this patient population in the postmarketing setting. In addition, the protocol was updated to address EMA recommendation to collect CD19 expression data to further characterize its association with liso-cel effectiveness. BMS proposed to collect such data via the registry-based study, and this was agreed.
2	08-Apr-2025	1-9	• Background information updated to add therapeutic context for follicular lymphoma patients; to reflect evolutions in the treatment landscape and to reflect available therapies in the third-line setting; and to include additional clinical trial data obtained in patients with FL treated with liso-cel as third line therapy • The primary objective has been reworded in 3 bullet points to improve readability. • Other minor revisions made eg, administrative changes, suppression of safety reports as a milestone of the study,	The reason for this amendment is to support an extension of the EU-approved indication of Breyanzi to include treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. As a consequence, the JCAR017-BCM-005 protocol was amended to broaden eligibility to the 3L+ relapsed or refractory follicular lymphoma grades 1 to 3A indication and expand the collection of safety and effectiveness data to this patient population in the real-world setting.

Table 5-1: Information on Protocol Amendments

Number	Date	Section of Study Protocol	Amendment or Update	Reason
			reworded Section 9.9 for improved clarity.	
3		1-9	• Background information updated to add therapeutic context for mantle cell lymphoma patients; to reflect evolutions in the treatment landscape and to reflect available therapies in the third-line setting; and to include additional clinical trial data obtained in patients with MCL treated with liso-cel as third line therapy	The reason for this amendment is to support an extension of the EU-approved indication of Breyanzi to include treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy, including a BTK inhibitor. As a consequence, the JCAR017-BCM-005 protocol was amended to broaden eligibility to the 3L+ relapsed or refractory mantle cell lymphoma indication and expand the collection of safety and effectiveness data to this patient population in the real-world setting.

6 MILESTONES

Milestones for this study are summarized in Table 6-1.

Table 6-1: Milestones

Milestone	Date
Date of Initial Registry-based study Protocol Submission to EMA as part of Marketing Authorization Application	29-Jun-2020
Date of Final Registry-based study Protocol Approval from EMA	01-Dec-2022[a]
Start of data collection[b]	17-Mar-2023[a]
Registration in the EU PAS Register	17-Mar-2023
Study Progress Updates	Per the PSUR cycle, according to the EURD list
Interim reports[c]	At Year 5, Year 10, and Year 15 or when the last patient is out of the registry-based study
Date of Study Completion[d]	Q4 2042
Date of Final Study Report Submission to EMA	Q4 2043

[a] Depending on the EC decision and protocol approval timeline.

[b] As the data collection in the EBMT Registry is independent of this study (secondary use of data), the start of data collection corresponds to the date from which data extraction starts. First data extraction for study JCAR017-BCM-005 will take place 3 months after protocol approval from EMA.

[c] Interim reports will be prepared at Year 5, Year 10, and Year 15 after EC decision date or when the last patient is out of the registry-based study.

[d] Fifteen years after reaching the defined patient number, no further data will be included in the study analyses.

EBMT, European Society for Blood and Marrow Transplantation; EC, European Commission; EMA, European Medicines Agency; EU PAS, European Union electronic Register of Post-Authorisation Studies; EURD, European Union Reference Dates; PSUSA, periodic safety update report single assessment; Q, quarter; TBC, to be confirmed.

7 RATIONALE AND BACKGROUND

7.1 Rationale

The purpose of this PASS is to further characterize the safety profile of liso-cel in the postmarketing setting.

This study will include patients from existing independent registries, such as, but not limited to, the European Society for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR).

The JCAR017-BCM-005 study will be part of the overall liso-cel Risk Management Plan (RMP) including any required regional Pharmacovigilance Plan (PVP) outside the European Union (EU).

7.2 Background

Non-Hodgkin lymphomas (NHLs) comprise a heterogeneous group of approximately 60 lymphoproliferative disorders originating in B lymphocytes, T lymphocytes, and natural killer (NK) cells.

In a population-based study in Sweden, 85% of NHL cases from 2000 and 2016 were B-cell lymphomas,[3] and diffuse large B-cell lymphoma (DLBCL) is the single most common form of NHL, accounting for 30% to 40% of all NHL cases[4,5]. Follicular lymphoma of any grade is the second most frequent B-cell NHL representing 17% of the cases.[3] The vast majority (85%) of the follicular lymphomas are FL grades 1 to 3A.[6]

The incidence rate of DLBCL in Europe from 2000 to 2002 was approximately 3.81 cases per 100.000 persons.[7] DLBCL is a heterogeneous disease with several histological and molecular subtypes and can either develop as a transformation from indolent lymphoid malignancies (eg, follicular lymphoma [FL], marginal zone lymphoma, chronic lymphocytic leukemia [CLL]), or as a de novo presentation of lymphoma. The largest subgroup is DLBCL not otherwise specified (NOS).

High-grade B-cell lymphoma (HGBCL) is a very aggressive form of large B-cell lymphoma that was introduced in the 2016 revision of the WHO classification of lymphoid neoplasms.[8] Most HGBCL cases harbor the dual rearrangement of MYC and BCL2 and/or BCL6 genes, accounting for 5% to 7% of all DLBCLs.[9]

Primary mediastinal large B-cell lymphoma (PMBCL) is a rare form of large B-cell lymphoma (6% to 10% of all NHLs) characterised by female predominance and primary mediastinal involvement.[10]

The incidence rate of FL of any grade in Europe from 2000 to 2002 was approximately 2.18 cases per 100.000 persons.[7] FL is a heterogeneous pathological entity that includes tumors derived from germinal center B-cells, both centrocytes and centroblasts. The t(14;18) translocation has been recognized as a genetic hallmark of FL and results in constitutive overexpression of the BCL-2 protein. The disease is characterized by diffuse lymphadenopathy, bone marrow involvement, splenomegaly, and other less common sites of extranodal involvement. Histologically, FL is classified as Grade 1, Grade 2, and Grade 3 (3A and 3B) depending on the percentage of the large lymphocytes present.[11]

Unless otherwise specified, the terms 'follicular lymphoma' (FL) and 'follicular lymphoma grade 3B' (FL3B) are used throughout the protocol to indicate, respectively, FL grades 1 to 3A and FL grade 3B. These terms correspond, respectively, to 'classic FL' and 'follicular large B-cell lymphoma' in the 5th edition of the WHO classification.[12]

Mantel cell lymphoma (MCL) is a B-cell malignancy and an aggressive form of non-Hodgkin's lymphoma (NHL), that comprises 6% of all NHL cases[13]. The disease occurs more commonly among elderly men, with a median age at diagnosis of 67 years, and a male to female ratio of 3:1.[14,15,16] The average age-adjusted incidence rate of MCL in Europe is estimated at 0.45 per 100,000 persons per year.[13]

7.2.1 Current Treatment Options

7.2.1.1 Large B-cell Lymphomas

The frontline treatment of advanced stage DLBCL is based on the combination of anthracycline-including polychemotherapy regimens and anti-CD20 monoclonal antibodies. R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) for 6 to 8 cycles is the recommended regimen for the initial treatment of DLBCL. In patients with intermediate-risk or high-risk DLBCL, a modified regimen of R-CHOP (in which vincristine was replaced with polatuzumab vedotin) has been shown to yield higher progression-free survival (PFS) and event-free survival rates compared to R-CHOP, although no survival benefit could be demonstrated.[17] The optimal frontline treatment for other forms of large B-cell lymphoma is currently unknown, and in most cases R-CHOP (or the dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin [R-EPOCH] variant) remains the regimen of choice. Involved-field radiotherapy is sometimes used as consolidation in the case of residual masses. Approximately 60% to 80% of patients with DLBCL, PMBCL, and FL3B (depending on age and other baseline risk factors) are expected to achieve long-term remission-cure with frontline immunochemotherapy. The outcome of HGBCL with standard immunochemotherapy is less favourable.

Approximately 10% to 40% of patients with DLBCL are refractory (ie, not able to achieve at least a partial response [PR]) to frontline immunochemotherapy or experience disease relapse after complete response (CR) was documented by positron emission tomography (PET)/computerized tomography (CT). Most relapses occur in the first 2 years after diagnosis, but up to one-fifth occur more than 5 years after treatment.[18]

Salvage treatment with non-cross resistant chemotherapy followed by autologous hematopoietic stem cell transplantation (ASCT) has long been considered the standard of care in this setting and has been associated with long-term survival/cure in approximately half of patients with first relapsed DLBCL. Subjects with DLBCL were prevalent in all studies investigating the efficacy of second-line salvage immunochemotherapy strategies: the extent of the efficacy of salvage regimens in histologies other than DLBCL is, therefore, uncertain. In the absence of dedicated options, patients with other large B-cell lymphoma histologies are usually treated according to the DLBCL salvage paradigm.

The role of salvage chemotherapy, usually administered for 2 to 3 cycles, is to reduce the burden of disease and determine residual chemosensitivity. Only patients who achieve CR/Deauville 4 PR according to PET/CT are eligible for ASCT, since patients with inadequate response to intensive salvage therapy (ie, with secondary refractory disease) have been shown not to benefit from transplant consolidation.

Several salvage immunochemotherapy regimens are currently available (eg, R-DHAP [rituximab, dexamethasone, high dose cytarabine, cisplatin], R-ESHAP [rituximab, etoposide, methylprednisolone, cytarabine, cisplatin], R-GEMOX [rituximab, gemcitabine, oxaliplatin], R-ICE [rituximab, ifosfamide, carboplatin, etoposide], R-GDP [rituximab, gemcitabine, dexamethasone, cisplatin]) and none was demonstrated to be clearly superior to the others.

In recent years, the treatment landscape has evolved with the conditional approval in the EU of tafasitamab (an anti-CD19 antibody used in combination with lenalidomide) and polatuzumab vedotin (an anti-CD79b monoclonal antibody conjugated to monomethyl auristatin E used in combination with bendamustine and rituximab) for the treatment of patients with relapsed/refractory (R/R) DLBCL who are not eligible to ASCT, representing possible alternatives in the salvage setting.

In addition, 3 chimeric antigen receptor T cell (CAR T cell) interventions are approved in the EU (axicabtagene ciloleucel [Yescarta®], tisagenlecleucel [Kymriah®], and lisocabtagene maraleucel [Breyanzi®]) and represent options for the treatment of adult patients with DLBCL and other large B-cell lymphoma histologies.[19,20,21] Among the approved indications, axicabtagene ciloleucel is indicated for the treatment of adult patients with PMBCL after 2 or more lines of systemic therapy, and lisocabtagene maraleucel for the treatment of adult patients with HGBCL, PMBCL, and FL3B who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy.

7.2.1.2 Follicular Lymphoma

The prognosis for FL has improved substantially over the past two decades since the introduction of monoclonal antibody therapies, such as rituximab, however, FL remains incurable.[22,23]

Treatment options in 1L include an anti-CD20 monoclonal antibody with or without chemotherapy.[24]

Approximately 20% to 30% of FL patients experience progression of disease within 24 months from diagnosis or the initiation of frontline therapy and are at high risk for poor long-term outcomes.[25,26,27]

Therapeutic options for 2L FL are similar to 1L.[18,24] For highly selected R/R patients, both ESMO[28] and NCCN guidelines[20] state that treatment may also include hematopoietic stem cell transplantation. In patients who experienced long remission after frontline therapy, guidelines suggest that the initial 1L regimen may be repeated in 2L therapy.[20] Lenalidomide plus rituximab combination (R^2) is approved by the FDA and EMA for treatment of patients with FL with at least one prior line of treatment (2L+ FL).[29]

Several therapies are currently approved in the US and the EU for treatment of patients with 3L+ R/R FL, however, standard of care for this patient population has yet to be defined.[30] Moreover, progression of the disease results in shorter intervals between each treatment and failure, reflecting a high unmet need in 3L+ R/R FL patients.[31]

PI3K inhibitors (idelalisib, duvelisib, copansilib) had been approved for treatment of patients with 3L+ R/R FL, however all three drugs have been subsequently withdrawn from the US market due to lack of confirmed clinical benefit.[32,33,34] Idelalisib and duvelisib are still approved in the EU for treatment of patients with R/R follicular lymphoma that is refractory to two prior lines of treatment.[35,36]

The BTK inhibitor, zanubrutinib, in combination with obinutuzumab, has received accelerated approval by the FDA and full approval by the EMA for the treatment of adult patients with R/R FL who have received at least 2 prior systemic therapies.[37]

The EZH2 inhibitor, tazemetostat, has received an accelerated approval by the FDA as a single agent for the treatment of patients with relapsed or refractory EZH2 mutation-positive FL who have received at least two prior systemic therapies or patients with R/R FL who have no satisfactory alternative treatment options.[38]

Novel T cell redirected therapies are also approved for treatment of R/R FL. The CD20 targeted bispecific antibodies, mosunetuzumab and epcoritamab, have an accelerated approval by the FDA and conditional approval by the EMA for treatment of patients with R/R FL with at least 2 prior lines of therapy.[39,40,41,42] The CD19 directed CAR-T cell products, axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel), are approved in the US and EU for treatment of patients with R/R FL (axi-cel: US accelerated approval for 3L+ R/R FL; EU conditional approval for 4L+ R/R FL; tisa-cel: US accelerated approval for 3L+ R/R FL; EU conditional approval for 3L+ R/R FL).[15,16,43,44] Liso-cel currently has accelerated approval for treatment of 3L+ R/R FL in the US, and in March 2025 it was granted approval for treatment of this patient population by the EMA.

7.2.1.3 Mantle Cell Lymphoma

No curative options exist for patients with MCL, and most patients require multiple lines of salvage therapy in their lifetime. Outcomes after each line of therapy progressively worsen:

median progression-free survival (PFS) and median OS, respectively, are 4.0 years and 9.7 years after 1L therapy; 14.0 months and 41.1 months after 2L therapy; 6.5 months and 25.2 months after 3L therapy; and 5.0 months and 14.4 months after 4L therapy[49].

As per the most recent National Comprehensive Cancer Network (NCCN) guidelines V5.2023 and ESMO guidelines recommend for symptomatic, young (< 65 years old) and fit patients immunochemotherapy regimens with or without a c BTKi and on the basis of the recent Phase 3 RCT TRIANGLE results47 followed by high-dose therapy and autologous stem cell transplantation, with the goal of obtaining longer remissions.

Due to the later onset of the disease, most patients are elderly at the time of diagnosis and are not suitable for transplant. For these patients preferred regimens include anti-CD20 antibodies in association with different agents (bendamustine or antracycline, lenalidomide, bortezomib) with or without a covalent BTKi. followed by optional maintenance therapy with rituximab[11].

Different cBTKi are available in US and Europe: acalabrutinib in combination with bendamustine and rituximab is approved for untreated MCL patients who are ineligible for autologous hematopoietic stem cell transplantation by both the FDA and the EMA, and has been granted traditional approval by the FDA in the R/R setting; zanubrutinib is available through accelerated approval only in US in R/R MCL while ibrutinib is currently approved only by the EMA in the R/R setting, as the FDA has withdrawn the accelerated approval which had been initially granted.

There is no single standard-of-care treatment for R/R MCL, the optimal approach/sequence to treat R/R MCL is yet to be defined, and there is a lack of data comparing the available treatment options in a randomized controlled fashion.

Several therapies are currently approved in the US and the EU for treatment of patients with R/R MCL. Bortezomib and lenalidomide have received regular approval from both the FDA and the EMA for the treatment of R/R MCL. Both were all licensed before the covalent BTKi, and therefore limited data are available on their efficacy in the post-BTKi setting.

Based on their improved efficacy both the ESMO and the NCCN guideline recommend the use of cBTKi in the 2L setting for patients who have not received a BTKi in the first line setting with or without venetoclax (not approved by either the FDA or the EMA for MCL)[48].

For patients previously treated with a cBTKi in the first or later lines of therapies, CAR-T cell therapy (e.g., brexucabtagene autoleucel or lisocabtagene maraleucel) is advised by both the ESMO and the NCCN guidelines. Pirtobrutinib, a non-covalent BTKi, can also be an option and has been approved after at least one line of therapy including a cBTKi by the EMA and after at least 2 lines of therapy including a BTKi by the FDA Immunochemotherapy remains an option for patients unsuitable for or relapsing after BTKi or CAR-T therapy, with regimen choice guided by prior exposure and patient fitness. BTKi rechallenge may be considered in cases of prior intolerance or after fixed-duration cBTKi therapy. Lenalidomide, with or without rituximab, may be used after other options have failed. Allogeneic stem cell transplantation can be considered for younger, fit patients if CAR-T therapy is unavailable or has failed[48].

7.2.2 Chimeric Antigen Receptor T Cell Therapies

T cell immunotherapy offers a promising approach for cancer treatment through harnessing the patient's own immune system to destroy malignant cells.[45] Studies with tumor vaccines,[46,47,48,49] immune checkpoint inhibitors,[50,51] and tumor-infiltrating lymphocytes[52] have demonstrated the potential of T cells to treat cancer.

The development of CAR T cell therapies represents a new targeted approach for treating malignancies. CAR T cells are recombinant receptors that target native surface antigens. The CAR is a fusion protein composed of several elements, including an extracellular binding domain (eg, single chain variable fragment [scFv], natural ligands, or fragment antigen binding) that binds the antigen on the cell surface, a transmembrane domain, and intracellular endodomains that provide activation signaling to the T cell after target cell engagement by the binding domain.[53]

Production of CAR T cells requires T cells to be genetically modified by ex vivo transduction using a recombinant viral (eg, lentiviral) vector containing the CAR ribonucleic acid sequence. Transduced T cells express the CAR on the cell surface and are effectively redirected toward recognition and lysis of the cells expressing the target antigen. Autologous CAR T cells may be generated and expanded from a patient's leukapheresis-derived peripheral blood mononuclear cells and subsequently cryopreserved. The CAR T cells can later be thawed and administered intravenously (IV) to the same patient.

CAR T cells directed against B-cell antigens have demonstrated promising antitumor activity across B-cell malignancies including B-cell NHL,[2,54,55] B-precursor acute lymphoblastic leukemia (ALL),[56,57] CLL,[58,59] and multiple myeloma.[60]

Treatment with CAR T cell therapies showed significant clinical response. Initial studies demonstrated complete remissions of 63% of children with R/R ALL[57] and 40% to 45% of initial complete response in adults with R/R NHL.[54,55]

Administration of cellular products such as CAR-expressing T cells can be associated with cytokine release syndrome (CRS), a systemic inflammatory response caused by the release of various cytokines.[61,62] Cytokine release syndrome manifests typically with characteristic clinical symptoms such as fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia. Symptoms and severity of CRS are highly variable, and management can be complicated by concurrent conditions. Cytokine release syndrome occurs in a variable fraction of patients after CAR T cell therapy, with incidences ranging from 35% to 93%. The variable incidence and severity of CRS between studies is likely due to differences in CAR construct, CAR T cell manufacturing, diagnosis, disease burden, eligibility criteria, and the systems used to grade CRS.[63]

CAR T cell therapy is associated with neurologic toxicities. Neurologic symptoms may appear within 4 weeks after CAR T cell infusion and include altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity. Focal neurologic deficits, seizures, encephalopathy, and acute cerebral edema have been reported, but are infrequent.[64] Rates and

severity of neurotoxicities vary, with severe (Grade ≥ 3) manifestations observed in 12% to 28% of patients receiving CAR T cell therapy.[2,54,55]

Recently, a panel of experts produced consensus recommendations and proposed new definitions and grading for CRS and neurotoxicity within the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, to better reflect CAR T cell-associated CRS.[61]

CD19-specific CAR T cells have a direct effect on B-cells, which leads to B-cell aplasia and consequently hypogammaglobulinemia. B-cell aplasia is an expected potential off-tumor, on-target toxicity. Prolonged B-cell aplasia has been observed in CD19-directed CAR T cell programs.[65,66]

Other toxicities that are important to assess in recipients of CAR T cells include prolonged time to recover blood counts and the development of infections.

Previous studies have shown increase of second malignancies after NHL which are potentially related to chemotherapy and radiotherapy, underlying immune dysfunction, or shared risk factors, such as immunodeficiency, selected viral infections (eg, human immunodeficiency viruses), lifestyle factors (eg, tobacco), and genetic susceptibility.[67] Thus, according to the Surveillance, Epidemiology, and End Results (SEER) registries, the Standardized Incidence Ratios of Second Primary Cancer for solid tumors (all sites) is 1.39 (1.33 to 1.45) in the US population of advanced DLBCL (2000 to 2015).

In the same population, the SEER registry is also highlighting an increased risk of Hodgkin and non-Hodgkin lymphoma, as well as acute myeloid leukemia (respectively, 9.3 [confidence interval (CI): 6.22 to 12.68]; 3.94 [CI: 3.47 to 4.47]; 8.85 [CI: 7.26 to 10.68]).

The potential impact of CAR T therapies on the risk of new malignancies following their use in all approved indications is not known. Because CAR T cells are a genetically modified product, there is a hypothetical possibility of insertional mutagenesis resulting in secondary malignancies. The modified T cells could become capable of autonomous proliferation, independent of binding tumor-associated antigen but this event has not been observed in the clinic.[68] In addition, the use of other therapies, such as lymphodepleting chemotherapy concomitant with CAR T cell therapy, can also lead to a risk of new malignancies. This risk requires patients to be monitored long term.

Moreover, it is also possible that modified T cells could lead to or exacerbate graft-versus-host disease (GVHD).[68]

7.2.3 Compound Background

Liso-cel is a genetically modified autologous cell-based product consisting of purified CD8+ and CD4+ T cells, in a defined composition, that have been separately transduced ex vivo using a replication-incompetent lentiviral vector expressing a CD19-specific CAR. The CD19-specific CAR consists of an scFv binding domain derived from a murine CD19-specific monoclonal antibody (mAb) (FMC63) and the 4-1BB and CD3ζ co-stimulatory/signaling domains. The truncated human epidermal growth factor receptor (EGFRt) protein is coexpressed with the CD19-specific CAR as a cell surface protein.

In vitro and in vivo studies have demonstrated the ability of liso-cel to proliferate, produce cytokines, and exhibit antitumor activity against CD19-positive cell lines and in tumor-bearing mice. The drug product is provided as CD8+ and CD4+ frozen T cell suspensions, which are thawed and infused separately. Administration of liso-cel is preceded by lymphodepleting chemotherapy, most commonly with low-intensity fludarabine and cyclophosphamide to increase the expansion, persistence, and antitumor activity of liso-cel.

The efficacy and safety of liso-cel were demonstrated in Study 017001, conducted under BB-IND 016506, a clinical trial for the treatment of patients with R/R NHL.[2]

8 RESEARCH QUESTION AND OBJECTIVES

8.1 Research Question

This PASS is a noninterventional study of large B-cell lymphoma, FL and MCL patients treated with liso-cel in the postmarketing setting to further investigate the research objective described in Section 8.2.

8.2 Research Objectives

8.2.1 Primary Objectives

- To characterize the incidence of selected adverse drug reactions (ADRs), as outlined in the Summary of Product Characteristics (SmPC), in patients treated with liso-cel in the postmarketing setting.
- To characterize the severity of the selected ADRs.

- To monitor for potential clinically important adverse events (AEs) that have not yet been identified as part of the liso-cel safety profile.

8.2.2 Secondary Objectives

- To assess long-term effectiveness in patients treated with liso-cel in the postmarketing setting.
- To assess the liso-cel safety and effectiveness profile in certain subgroups including but not limited to:
  - large B-cell lymphoma subtypes (eg, diffuse large B-cell lymphoma [DLBCL] not otherwise specified [NOS], high grade B-cell lymphoma [HGBCL], primary mediastinal B-cell lymphoma [PMBCL], follicular lymphoma Grade 3B [FL3B])
  - NHL histology (LBCL, FL, MCL)
  - number of prior lines of systemic therapy
  - geographical regions (eg, Europe)
  - subjects aged ≥ 75 years
  - subjects with comorbid conditions (eg, renal impairment, reduced cardiac function)
  - subjects with secondary central nervous system (CNS) involvement
  - subjects with Eastern Cooperative Oncology Group (ECOG) performance score ≥ 2
  - possible prognostic factors (eg, high-risk international prognostic index [IPI])
  - subjects previously exposed to anti-CD19 therapy
  - subjects with low pre-leukapheresis ALC ($< 0.3 \times 10^9$/L)
  - subjects treated with out-of-specification (OOS) product

8.2.3 Exploratory Objective

- To characterize the association between liso-cel effectiveness and CD19 expression obtained prior to liso-cel infusion.

9 RESEARCH METHODS

9.1 Study Design

9.1.1 Study Design

This study is designed as a noninterventional registry-based cohort study that is based on secondary use of data from existing independent registries of patients with lymphoma who were treated with liso-cel therapy in the postmarketing setting, which includes patients treated with OOS product.

Data from at least 750 patients with a target of 1000 patients – of which a minimum of 200 patients will come from European countries – will be collected until death or withdrawal of consent or up to 15 years, whichever occurs first.

This PASS is expected to require up to 5 years to select the planned number of patients globally.

This study is a single-cohort study in which all patients are exposed to liso-cel. Hence, its design does not involve any hypothesis testing regarding a potential difference (in safety or effectiveness) between exposed and unexposed patients.

Secondary malignancies must be reported to the MAH by the treating physicians in order to expedite AE reporting. In the event that a secondary malignancy of T cell origin is suspected, the MAH should be contacted to obtain instructions on the collection and transfer of a tumor tissue sample for testing in a separate process, outside of this PASS. In the postmarketing setting, the MAH will offer transgene assay service testing for all secondary malignancies of suspected T cell origin where a sample is available, as a routine pharmacovigilance measure to ensure gathering the most information possible for clinical assessment of the reported spontaneous case.

9.1.1.1 Primary Safety Endpoint(s)

Incidence and severity of selected ADRs post liso-cel infusion:

- Secondary malignancies
- Cytokine release syndrome (CRS) all grades
- Neurotoxicities all grades
- Prolonged cytopenias
- Pregnancy outcome
- Other AEs considered related to liso-cel treatment (Grade ≥ 3, where applicable):
  - hypogammaglobulinemia (if available)
  - tumor lysis syndrome (TLS)
  - infections
  - organ toxicities
  - others (eg, aggravated GVHD)
  - any clinically important AE occurring after liso-cel infusion not yet identified as part of the liso-cel safety profile, where a clinically important AE is defined as any AE not previously described in the Summary of Product Characteristics and deemed potentially clinically important based on available AE information (verbatim, severity grading). Classification will be determined on a case-by-case basis through review by the Sponsor/MAH.

9.1.1.2 Secondary Effectiveness Endpoint(s)

- Overall response rate (ORR)
- Complete response rate (CRR)
- Duration of response (DoR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Time to next treatment (TTNT)

9.1.1.3 Exploratory Endpoint(s)

- CD19 expression in tumor biopsies prior to liso-cel infusion

9.2 Setting

This noninterventional cohort study will be based on secondary use of data that are collected from existing independent registries, such as, but not limited to, the EBMT and the CIBMTR. Both registries use electronic Registry Case Report Forms (CRFs) onto which data may be entered directly by the treating centers.

All patients included in the EBMT and the CIBMTR registries are treated by their physicians according to real-world clinical practice. Physicians are trained to identify and approach patients treated with at least 1 dose of liso-cel for an approved large B-cell lymphoma indication according to the EMA SmPC, including DLBCL, HGBCL, PMBCL, FL3B, FL and MCL to obtain their written informed consent to transfer their pseudonymized patient-level data to the EBMT or the CIBMTR registries and to be shared with competent health authorities, Marketing Authorization Holder (MAH), and other parties in line with the signed informed consent forms (ICFs).

9.2.1 Eligibility Criteria

All patients who meet the following inclusion criterion will be selected from the registries:

- Patient must have been treated with at least 1 infusion of liso-cel in the postmarketing setting for an approved indication according to the EMA SmPC, including large B-cell lymphomas (DLBCL, HGBCL, PMBCL, and FL3B), FL and MCL indications. Patients treated with OOS product will also be eligible.

Patients who meet the following exclusion criterion will not be eligible for selection from the registries:

- Patients known to be participating in investigational studies at the time of liso-cel infusion.

9.3 Variables

The following information will be recorded and used within this study:

Table 9.3-1: Variables

Classification	Category	Variable	Description
Baseline (at infusion date)	General Identifiers	Patient Code/ID	Unique de-identified ID for patient
		Reporting Center (RC) Name/ID	Center name or ID reporting to the registry
		Manufacturing Site (MFS) Name/ID	Site name or ID producing the CAR T product
		Apheresis Center (AC) Name/ID	Center name or ID conducting leukapheresis
		Site of Care (SC) Name/ID	Center name or ID treating patient and infusing the CAR T product
Baseline	Product Information and Linking Identifiers	Product Name	Name of CAR T product
		Product Lot Identifier (Join ID)	Unique leukapheresis event identifier corresponding to 1 Breyanzi lot
		CD4+ Component Lot Number	Join ID with suffix for the CD4+ component
		CD8+ Component Lot Number	Join ID with suffix for the CD8+ component
		Product Quality: OOS	Product: out of specification, yes/no
Baseline	Key Treatment Processes and Timing	Patient Registering Date	Date patient was registered into the registry database by the RC
		Leukapheresis Date	Date blood was collected at the AC
		Pre-leukapheresis ALC	ALC count prior to leukapheresis
		Blood Shipment Date	Date blood was shipped from the AC to the MFS
		Blood Arrival Date	Date blood arrived at the MFS
		Manufacturing Start Date	Date MFS started production of CAR T
		Manufacturing End Date	Date MFS completed production of CAR T
		Product Shipment Date	Date CAR T was shipped to the SC
		Product Receipt Date	Date CAR T arrived at the SC
		Lymphodepleting Therapy Date	Date when lymphodepleting therapy started at SC
		Infusion Date	Date when CAR T was infused to the patient at the SC
		Product Infusion Count	Infusion counting number and total number of infusions
		Infused dose	Total number of cells or volume infused for each of the CD8+ and CD4+ cell components

Table 9.3-1: Variables

Classification	Category	Variable	Description
		Diagnosis Date	Date when primary disease was diagnosed
		Last Contact Date	Date when patient was the last time in contact with the SC
		Safety Assessment Date	Date of any safety assessments finding (as listed in the safety section)
		Effectiveness Assessment Date	Date of any effectiveness assessments finding (as listed in the effectiveness section)
Baseline	Demographics	Age	Age at infusion (years)
		Weight	Body weight at infusion (kg)
		Height	Body height at infusion (cm)
		Sex	Sex of patient
		Country	Country of the infusion center
		Region	Region of treatment: North America/Europe/Japan/Rest of the World
Baseline	Clinical Variables (Disease History/ Prior Therapy/ Infusion Related)	Karnofsky Performance Score	Karnofsky performance score at infusion
		ECOG Performance Score	ECOG performance score at infusion
		Disease History/Comorbidity	Comorbidity and organ impairment (eg, cardiac, hepatic, obesity, pulmonary, renal, diabetes, solid tumor, and others) at infusion
		Prior Therapy 1 Lines	Number of prior therapy lines
		Prior Therapy 2 List	Names of prior therapies (systemic therapies, standard regimens, including anti-CD19 therapy)
		Prior Therapy 3 HCT	Number of prior HCTs
		Prior Therapy 4 HCT Type	Types of prior HCTs (eg, autologous, allogeneic)
		Disease Status 1 Primary Disease	Primary disease (eg, NHL) and disease status (eg, relapsed or refractory) at infusion
		Disease Status 2 Disease Stage	Lymphoma staging classification (eg, Ann Arbor Stage I-IV) at diagnosis or infusion
		Disease Status 3 Extranodal Involvement	Extranodal involvement (eg, bone marrow, liver, lung, CNS, and others) at infusion

Table 9.3-1: Variables

Classification	Category	Variable	Description
		Disease Status 4 Lymphoma Classification	Disease subtype (eg, DLBCL NOS, HGBCL PMBCL, FL3B, FL, MCL) at diagnosis
		Disease Status 5 Cytogen. FISH	Double/triple hit (c-MYC, BCL-2, BCL-6 rearrangements) identified via FISH at diagnosis
		Disease Status 6 Cytogen. Karyotyping	Cytogenetic testing via karyotyping at diagnosis
		Disease Status 7 Prognostic Score	Prognostic score (eg, IPI) at diagnosis and/or infusion
		Disease Status 8 CD19 Expression	Assessment of CD19 expression when available (ie, positive, negative); tissue (ie, bone marrow, lymph node, other tissue); timing (eg, at time of diagnosis, at time of disease transformation, at time of relapse, at time of infusion, as available); method (ie, IHC or flow cytometry)
		Lymphodepleting Treatment	Types and names of lymphodepleting chemotherapy agents
Outcome (reported at 100 days, 6 months, yearly)	Safety	Secondary Malignancies (SM)	Subsequent neoplasms assessment and types of SM reported during follow-up
		Cytokine Release Syndrome 1 Presence	Assessment and presence of CRS reported during follow-up
		Cytokine Release Syndrome 2 Grade	CRS grade
		Cytokine Release Syndrome 3 Symptoms	CRS symptoms (eg, fever, hypotension, hypoxia)
		Cytokine Release Syndrome 4 Therapy	CRS therapy: intravenous fluids, vasopressors, positive pressure vent support, other therapy (eg, but not limited to tocilizumab), CRS resolution date
		Neurotoxicity (NT) 1 Presence	Assessment and presence of NT reported during follow-up
		Neurotoxicity 2 Grade	NT grade
		Neurotoxicity 3 Symptoms	NT symptoms (eg, aphasia, consciousness, dysphasia, seizure, paraparesis, cerebral edema, hallucination, tremors, other neurologic symptoms)
		Neurotoxicity 4 Therapy	NT therapy: antiepileptic and other therapy given, NT resolution date
		Prolonged Cytopenia 1 Presence	Absolute Neutrophil Count < 500/mm^3, platelet count < 20× 10^9/L
		Prolonged Cytopenia 2 Recovery	Neutrophil and platelet recovery

Table 9.3-1: Variables

Classification	Category	Variable	Description
		Hypogammaglobulinemia 1 Presence	Assessment and presence of hypogammaglobulinemia during follow-up (if available)
		Hypogammaglobulinemia 2 Therapy	Hypogammaglobulinemia therapy (immunoglobulin replacement) and resolution
		Tumor Lysis Syndrome 1 Presence	Assessment and presence of TLS reported during follow-up
		Tumor Lysis Syndrome 2 Grade	TLS grade
		Organ Toxicity Grade ≥ 3	AE/symptoms/type at heart, gastrointestinal, kidney, liver, lungs, musculoskeletal, neurologic reported during follow-up
		Aggravated GVHD	Information regarding chronic and acute GVHD
		Infections	Types and sites of serious (ie, requiring treatment) infection reported during follow-up (1st-5th reported infection)
		Pregnancy Outcome	Pregnancy reported during follow-up for female and for male partner
		Concomitant Medication	Other systemic therapy given for maintenance or consolidation reported during follow-up

Table 9.3-1: Variables

Classification	Category	Variable	Description
Outcome (reported at 100 days, 6 months, yearly)	Effectiveness	Best Overall Response 1 CT Resp. Ass.	Assessment of response (and best overall response) based on CT
		Best Overall Response 2 PET Resp. Ass.	Assessment of response (and best overall response) based on PET
		Relapse and Progression 1 Outcome	Outcome of assessment for relapse or progression
		Relapse and Progression 2 Therapy	Therapy given for treatment of relapse or progression
		Progression Status	Status of progression
		Relapse Status	Status of relapse
		Cause of Death	Primary cause of death and contributing causes of death #1 to #4
		Survival Status	Survival status at last contact

CT, computerized tomography; Cytogen., cytogenetic; FISH, fluorescence in situ hybridization; HCT, hematopoietic cell transplantation; ID, identifier; PET, positron emission tomography; Resp. Ass., respiratory assessment.

9.4 Data Sources

Baseline and clinical outcome data for this noninterventional secondary use of data study will be retrieved from existing independent registries, such as, but not limited to, the European Society for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR). Treatment centers across the United States (US), Europe, and other countries that have an agreement with the independent registry holders will report data to the registries. The registry holders will maintain direct interactions with the participating treatment centers related to data collection and quality assurance activities. Data collection in the registries will be done irrespective of this study and therefore the MAH will not have any registry-related relationships with the participating treatment centers. At regular intervals (eg, quarterly), pseudonymized patient-level data from the registry holder databases will be shared with the MAH, as agreed upon in contractual agreements between the MAH and the registry holders. A diagram of the communication flow is presented in Figure 9.4-1.

Figure 9.4-1: Data Sources, Lines of Communication, and Data Processing

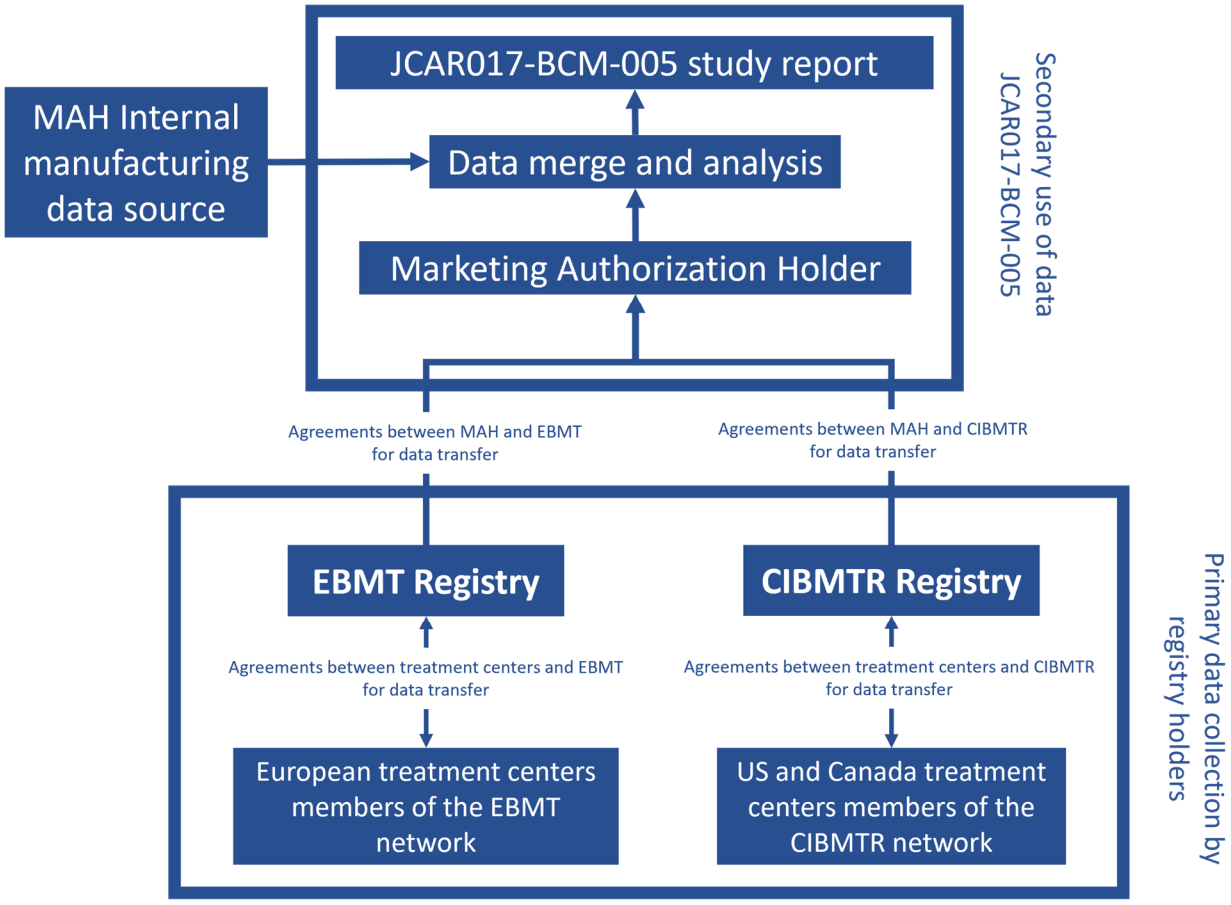

Diagram showing the current lines of communication between the MAH, registry holders, and treatment centers. The protocol provides the flexibility to include other data sources in the future, if available and required.

In addition to data retrieved from the registries, product quality data will be obtained from internal sources (eg, MAH internal manufacturing database) in order to define if patient was treated with a liso-cel in-specification product or OOS product.

Data obtained from the registries and data obtained from internal sources (eg, internal manufacturing database) will be linked via a set of unique identifiers including:

- JOIN identifier (ID) (unique leukapheresis event identifier corresponding to 1 lot)
- CD4+ component lot number (JOIN ID suffix)
- CD8+ component lot number (JOIN ID suffix)

The data will be integrated into 1 internal data system built and managed by the MAH.

Associated responsibilities are the following:

- Treatment centers are responsible for the accuracy and completeness of the data reported to the registries.
- The registry holders are accountable for the quality of the data held within the registry databases. Specifically, the registry holders are responsible for data collection, data management activities, monitoring activities, and overall quality management. They are also responsible for the development of the patient ICF, and for obtaining the necessary health authority and ethical committee approvals for conducting their registry. In addition, the registry holders are responsible for conducting site training for their respective registry and will maintain constant contacts with the treatment centers.
- The MAH is responsible for the design and oversight of the analyses described in this protocol and has the responsibility for the conduct of this PASS.

9.5 Study Size

Since this is a single-arm noninterventional cohort study with no comparisons and no statistical hypothesis testing, no formal powered sample size calculation is possible. Instead, a fixed number of at least 750 patients from registries is used based on pragmatic nonstatistical reasons, which is considered feasible within the estimated 5-year selection period. The study sample size is supported from a statistical point of view by providing precision estimates (see below).

Precision estimates, based on incidences taken from the literature, are provided by calculating exact 95% Clopper Pearson CIs based on a binomial distribution (see table below).

Assumed incidences for secondary malignancies were taken from reported incidences of an advanced DLBCL population in SEER 18 regions comprising a total of 25,452 patients.[1]

Thus, in conclusion, if similar incidences are observed in this study, this would provide sufficient precision for a meaningful interpretation of the observed incidences.

Table 9.5-1: Reported Incidences of Secondary Malignancies, CRS, and Neurotoxicity in DLBCL

Data Source	Description	No. of Patients	Observed Incidence	Incidence Proportion	Clopper Pearson 95% CI lower [for 750 patients]	Clopper Pearson 95% CI upper [for 750 patients]
SEER 18 Regions, 2018[1]	Incidence of non-Hodgkin Lymphoma	25,452	246	0.010	0.004	0.019
	Incidences of secondary malignancies at all sites	25,452	1,950	0.077	0.058	0.097

DCCPS, Division of Cancer Control and Population Sciences; No., number.
Source: SEER Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 18 Regs/National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission.[1]

9.6 Data Management

As this study is based upon secondary use of data, data management activities will be the responsibility of the registry holders.

The databases and software used by the EBMT during the course of the study meet the internationally recognized ethical and scientific quality requirements for designing, conducting, recording and reporting studies involving human subjects. Treatment centers need to be registered to the EBMT Registry system. This registration generates a unique EBMT Center Identification Code (CIC) and includes training on the data collection system. Treatment centers initiate patient reporting through the generation of an EBMT Registry Unique Identification Code, which is unique to every patient. In addition, treatment centers may enter an internal Unique Patient Number (UPN). The Therapy Indication Form will identify that the patient is a recipient of liso-cel and triggers a series of forms appropriate for the specific indication that will be under that unique identification code (UIC).

FormsNet^{TM} 3 (FN3), the CIBMTR's web-based data collection system, is compliant with the US database security requirements established by the Health Resources and Services Administration Office of Information Technology and with the Food and Drug Administration (FDA) 21 Code of Federal Regulations 11. Treatment centers need to be registered as a CIBMTR member and sign a Master Healthcare Data Agreement (MHA) and a Sample Submission Agreement to allow the transfer of data between organizations (CIBMTR and treatment center). Upon MHA completion, treatment center staff are provided access to FN3, and are provided training on the CIBMTR data collection processes including the use of the FN3 system. Treatment centers initiate patient reporting through the FN3 generation of a CIBMTR Research Identification (CRID) number, which is unique to every patient. The Therapy Indication Form will identify that the patient is a

recipient of liso-cel and triggers a series of forms appropriate for the indication. With the CRID, the patient's record can be tracked over time as well as multiple indications. In addition, data are managed through a role-based security model and the CIBMTR data collection, data storage, and data sharing systems are externally audited every year.

At regular intervals (eg, quarterly), the registry holders will provide pseudonymized patient-level data sets to the MAH through a secure file transfer protocol. Data from the 2 registries will be exported following internationally agreed data standards for clinical data sharing (eg, Study Data Tabulation Model [SDTM]-Clinical Data Interchange Standards Consortium [CDISC]) and then combined into Analysis Data Model (ADAM)-like data sets including derived variables to allow consistent and periodic analyses. These data sets will include the characteristics, outcome variables and other covariates. Data dictionaries will be prepared by the registry holders to describe all variables included in the study and their possible values.

Data collected from internal sources will be managed by the MAH through a validated laboratory information management system. In addition, regular comparison and validation of the unique identifiers linking the internal and external data sources of the registries will be conducted jointly by the MAH and the registry holders.

9.7 Data Analysis

In this noninterventional cohort study, results will be analyzed and reported descriptively; no formal hypothesis testing is intended.

Confidence intervals will be presented as 2-sided 95% intervals unless specified differently for specific analyses.

Summary statistics will consist of the number and percentage of patients in each category for discrete variables, whereas for continuous variables the sample size, mean, median, standard deviation, minimum, and maximum will be given.

All analyses will be carried out for the defined subgroups per histology, separately.

A detailed statistical analysis plan (SAP) will be finalized before the first analysis.

9.7.1 Analysis Sets

Due to the noninterventional nature of the study, commonly used analysis sets like the intent to treat set or the per protocol set are not defined in this study.

- The **Infused Set (IS)** is defined as all patients selected from the registry and meeting the study eligibility criteria, where baseline and disease classification information is available.
- The **Safety and Effectiveness Set (SES)** is defined as all patients from the IS with postinfusion safety or effectiveness information.

9.7.2 Analysis of Study Conduct and Study Discontinuation

An adapted CONSORT diagram will be provided for documenting the number of patients at each reporting schedule. It will also present the patients' situation with regards to their participation in the study and, if relevant, the reason why and when they stopped.

The total number of patients selected from the registries and used within the study, as well as the number and percentage of patients, will also be presented by country and center.

Patient disposition will be summarized and defined as patients who receive liso-cel and are reported to the corresponding registries with either ongoing follow-up, completed follow-up at 15 years or discontinued postinfusion follow-up due to death.

9.7.3 Baseline Data: Demographics, Disease History and Prior Therapies

Treatment centers will be encouraged by the registry holders to register patients into the registry database from 2 weeks prior to the liso-cel infusion to 6 months after infusion. Baseline data are retrospectively reported by data managers after the administration of liso-cel and are collected only once. All information, including any medical history and measurements done prior to the administration of liso-cel, becomes available in the registry as baseline data.

The baseline data will be summarized using descriptive statistics. Individual patient listings will also be provided to support the summary tables. The number and percentage of patients in each of the categories, as listed in Section 9.3 will also be given.

The following baseline data will be presented separately by histology:

- **Demographics:** Demographic information collected at baseline will be presented using descriptive statistics.
- **Disease History/Status:** Information regarding disease characteristics at diagnosis (eg, lymphoma histology, cytogenetic abnormalities, prognostic information such as IPI score) and status at time of infusion (eg, disease status, ECOG performance score, CNS involvement, comorbidity) will be summarized by frequency counts. The frequency of patients with at least 1 comorbidity, as well as frequency counts of different comorbidities will be presented.
- **Prior Therapy/Prior Medications:** Number of lines of prior therapies will be presented using descriptive statistics. Number of lines of prior therapies in category will be described as frequency counts. A frequency tabulation of the number of patients with the different types of previous therapies (eg, chemotherapy, radiotherapy, surgery) will be given. Also, a frequency tabulation of whether patient had prior hematopoietic cell transplantation (HCT) and the types of prior HCTs will be given.
- **Lymphodepleting Treatment:** A frequency tabulation of the list of lymphodepleting agents will be given.

9.7.4 Effectiveness Analysis

9.7.4.1 Analysis of the Secondary Effectiveness Endpoints

- Effectiveness endpoints will be analysed separately for LBCL, FL, and MCL because these histologies represent distinct clinical entities with different disease biology, prognosis, and treatment paradigms. **Overall response rate (ORR):** ORR is the proportion of patients with a best overall response of CR or PR, where best overall response is defined as the best disease response recorded from liso-cel infusion until disease relapse or progression or start of new anti-cancer therapy, whichever happens first. If best response is collected by both CT and PET methods, best response per PET overrules best response per CT.

- **Complete response rate (CRR):** CRR is the proportion of patients with a best overall response of CR, where best overall response is defined as the best disease response recorded from liso-cel infusion until disease relapse or progression or start of new anti-cancer therapy, whichever happens first. If best response is collected by both CT and PET methods, best response per PET overrules best response per CT.
- **Duration of response (DoR):** DoR is defined as the time from the date of first documented disease response (CR or PR) to the date of first documented progression or first documented relapse, or to date of death due to any cause, whichever happens first. Patients who are alive and didn't experience disease progression, relapse or death before last contact date will be censored at that time, but no censoring will be done for additional treatment.
- **Progression-free survival:** PFS is defined as the time from the date of first liso-cel infusion to the date of event defined as the first documented relapse or progression or death due to any cause, whatever happens first. Patients who did not reach such events before the last contact date will be censored at that time, but no censoring will be done for additional treatment.
- **Overall survival (OS):** OS is defined as the time from the date of first infusion to the date of death due to any cause. All patients will be followed for survival information, regardless of whether they receive additional treatment postinfusion. Patients who are alive at last contact date will be censored at that time, but no censoring will be done for additional treatment. OS will be calculated according to the formula:

  OS (months) = (date of death or censoring – infusion date + 1) / 30.4375.

- **Time to next treatment (TTNT):** TTNT is defined as the time from the date of liso-cel infusion to next treatment of the primary disease (excluding consolidation and maintenance therapies). Patients who did not receive any new treatment for the primary disease before the last contact date or before death will be censored at the last contact date or death date. TTNT will be calculated according to the formula:
  - TTNT (days) = date of start of the next therapy line or censoring – infusion date + 1
- **Time-to-Event (TTE) Analysis:** For DoR, PFS, OS, and TTNT, Kaplan-Meier (KM) estimates and the associated 95% CIs of the median, 25th and 75th percentile will be presented. The 2-sided 95% CIs will be computed using the log-log transformation. The survivor function will be displayed graphically using a KM curve.

9.7.5 Safety Analysis

9.7.5.1 Analysis of the Primary Safety Endpoints

The primary endpoints are the incidence and severity of the following selected AEs or toxicological symptoms reported post liso-cel infusion.

- Secondary malignancies
- Cytokine release syndrome all grades
- Neurotoxicity all grades
- Prolonged cytopenias
- Pregnancy outcome
- Other AEs considered related to liso-cel treatment (Grade ≥ 3, where applicable):
  - hypogammaglobulinemia (if available)

- tumor lysis syndrome
- infections
- organ toxicities
- other (eg, aggravated GVHD)

The primary endpoints will be analyzed and reported as described in Section 9.7.5.2 (below). Furthermore, suitable measures (incidence proportions and incidence rates) will be calculated with the appropriate time periods and methods. Analyses will be carried out without accounting for competing risks as well as accounting for competing risks using the cumulative incidence function method. Details are described in the SAP.

Safety endpoints will be analyzed using the combined set of all indications (LBCL, FL, MCL) to maximize statistical precision and favor detection of safety signals. This approach is justified by the same exposure to liso-cel and consistent safety profile reported across indications with the need for detection of rare events. Subgroup analyses by histology will be performed as appropriate to explore potential differences in risk.

9.7.5.2 General Handling and Analysis of Symptoms or Adverse Events

The collection of safety data in the registries is specific to certain symptoms of toxicity associated with CAR T cell therapy and recorded as safety outcomes. These include CRS, neurotoxicity, hypogammaglobulinemia, TLS, infections, prolonged cytopenias, organ toxicities and secondary malignancies. All, except for the secondary malignancies, are collected on a calendar format in an aggregate and summarized form based on the prior reporting period. Secondary malignancies, pregnancies and any deaths are reported on an event driven form upon knowledge at the treatment center.

The incidence of organ toxicities will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). Organ toxicities will be graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 or higher. Only organ toxicities of Grade 3 (severe), Grade 4 (life-threatening), and Grade 5 (death) will be summarized in reports. A patient who reports multiple occurrences of organ toxicities with the same SOC and PT is counted only once using the maximum severity grade for summaries. If a patient experiences the same organ toxicity more than once with different grades, then the event with the highest grade will be tabulated in "by grade" tables. If a patient experiences multiple organ toxicities under the same PT and SOC, then the patient will be counted only once for that PT (SOC).

The incidence of each adverse event of interest and of most frequent AEs (≥ 10%) will be summarized using the number and percentage of patients experiencing the event. Exact 95% Clopper Pearson CIs will be provided for the percentages.

Adverse Events will be reported according to the following structure:

1) **Overall Summary of Organ Toxicities/Symptoms:** Summaries of AEs will be produced overall as described above.

2) **Summaries by System Organ Class and Preferred Term:** Summary tables by SOC and PT of the number of events and the number, percentage, and exact 95% Clopper Pearson CIs for patients having events will be presented separately for each of the event types.
3) **Summaries by System Organ Class, Preferred Term, and Highest Grade:** Events will be presented by SOC, PT, and highest grade. Number, percentage, and exact 95% Clopper Pearson CIs of patients for each of the event types will be presented using patient's maximum grade.

Other toxicological symptoms, recorded using free text fields, are coded using SOC and PT based on the most recent version of MedDRA.

9.7.6 Analysis of the Exploratory Endpoint

The relationship between the different binary effectiveness endpoints (ORR and CRR) and CD19 expression (negative vs positive) will be assessed using separate Fisher's exact tests of independence. Odds ratios will be provided as a measure of effect size. Patients with no response assessment will be included in the analysis as non-responders. The relationship between time to event effectiveness endpoints (DoR, PFS, and OS) and CD19 expression (negative vs positive) will be assessed using separate log-rank tests. A hazard ratio obtained from a Cox Proportional-Hazards model will be provided as a measure of effect size. An alternative to the log-rank test will be chosen in the event that the data do not support the proportional hazards (PH) assumption based on the observed pattern of non-PH.

CD19 expression assessed at the most recent timepoint prior to CAR T cells infusion (eg, at diagnosis or at time of disease transformation) will be assumed to reflect CD19 expression at time of CAR T cells infusion (ie, it will be assumed that no loss or gain of CD19 expression occurred between the 2 timepoints). Patients who are positive for CD19 expression at any timepoint prior to infusion will be assumed to have been positive for CD19 expression at the time of infusion.

9.8 Quality Control

9.8.1 Quality Control Performed by the EBMT and the CIBMTR Registries

Data in the PASS will be managed according to the processes of the EBMT and/or the CIBMTR. The quality control details will be further described in the operational plans of the EBMT and/or the CIBMTR, which will be written for this study specifically.

The EBMT and/or the CIBMTR will secure the data in line with local applicable regulatory law and procedures. Access will be limited to authorized individuals only. Controls, such as document encryption, will be used to ensure the authenticity, integrity, and confidentiality of electronic records when transmitted over open systems (eg, the internet). The study data will be adequately backed up at regular intervals.

All individuals at treatment centers responsible for the integrity of the data will be trained by the EBMT and/or the CIBMTR staff on the requirements of the PASS.

For data stored at the corresponding registries, the standard processes of the EBMT and/or the CIBMTR will be followed. This procedure will ensure the quality of the data in the registry and will ensure that the data are reviewed and queried on an ongoing basis to support data accuracy

and completeness. In addition, the system will contain automatic edit checks that validate data entry according to prespecified standards, as well as regular data review by data management and monitors that will generate manual edit checks to ensure the quality of data.

Furthermore, the data from the EBMT and/or the CIBMTR registries will be checked against source documents for 10% of patients; this approach will be risk-based and can be done remotely and/or at the treatment center. Details will be documented in the specific operational plans of both organizations.

9.8.2 Quality Control Performed by the Marketing Authorization Holder

The MAH retains the right to audit the study data and processes of the EBMT and the CIBMTR at any time if required. Findings of such audits will be documented and filed. If necessary, appropriate measures will be taken if issues are detected at audits.

The MAH will develop and implement an internal platform to store all data obtained in the frame of this study from external sources. The source verification is the responsibility of the registry holders as described in Section 9.8.1 and Section 9.8.3. However, the MAH will implement quality control measures to ensure data integrity and suitability prior to each analysis. Specifically, the MAH will develop a data quality assessment plan with specific checks to gauge the quality of the received registry data. The results of the assessment will be documented in a data quality assessment report produced prior to the interim and final analyses.

Any data manipulation (eg, merging, transformation, calculations) will be documented according to appropriate data management practices used by the MAH for clinical trial data (eg, programming data specifications, data management plan) using appropriate quality control measures.

9.8.3 Study Center Monitoring and Source Data Verification

Treating physicians, or appropriate designees at treatment centers, will enter data online into the registry-owned databases. All data will be stored securely and confidentially. The data will be electronically verified using programmed edit checks.

Data quality control reports will be run by the EBMT and/or the CIBMTR to check for missing or incorrect data on a regular basis.

Remote and/or limited onsite monitoring, to ensure source data verification, will be performed by the EBMT and/or the CIBMTR according to their standard procedures and regulatory recommendations.

Regular onsite monitoring visits are not planned by the EBMT and/or the CIBMTR; however, a risk-based approach with remote and limited onsite monitoring will be performed by the EBMT and/or the CIBMTR to ensure the data integrity.

A representative or delegate from the EBMT and/or the CIBMTR may visit the centers that participate in the study at periodic intervals to review medical records and source documentation. During remote/onsite audit of data, patients' source documents and all other study documentation

will be inspected/reviewed by the EBMT and/or the CIBMTR representative or delegate according to a prespecified data monitoring plan.

9.9 Limitations of the Research Methods

As this is an observational PASS based upon secondary use of data, Sponsor has no influence on the quality of the original data collected in the primary source. In addition, missing data are inevitable, because certain variables may not have been routinely recorded in the patient medical charts. Furthermore, data will also be missing due to gaps in the follow-up (as routine scheduled visits cannot be mandated in an observational study), and loss to follow-up, especially in this study with a planned duration of 15 years. Details of how missing data are handled are also outlined in the SAP.

A considerable amount of missing data could significantly bias time to event analyses, as well as analyses quantifying a duration. In the EBMT and the CIBMTR registries, data are recorded at baseline, 100 days, 6 months, and then yearly. Thus, owing to center-specific different levels of compliance, a high variability in the recording of assessment dates is to be expected.

If a significant number of patients are lost to follow-up early on, it will not be possible to monitor long-term AEs. Loss to follow-up of a significant number of patients may also impact the ability to (1) accurately estimate incidence rates and/or (2) generalize to the source population.

Centre or HCP participation, as well as absence of patients' consent to share data with the Sponsor, might all lead to a biased study population. This would impact the generalizability of the study findings and representativeness of the sample with respect to the target population. To minimize this issue, centers are requested to ask every patient treated with liso-cel to have their data shared with the registry holder and with the Sponsor The MAH has implemented a healthcare professionals (HCPs) educational program in Europe that informs HCPs that patients who receive liso-cel are expected to be enrolled in a registry and to be followed in the registry in order to better characterize the long-term safety and effectiveness profile of liso-cel. In addition, the registry holders will provide continuous support and regular training to the treatment centers and will maintain constant contacts with them, emphasizing the importance and purpose of the data collection, and encouraging them to enter baseline patient data promptly and to capture follow-up data continuously. The registry holders will compensate participating treatment centers for data entry into the registries.

Nevertheless, not all patients will consent to have their data sent to the EBMT or the CIBMTR registries, possibly resulting in a biased sample of patients. A high rate of attrition (particularly if mortality is not captured well) could bias the results. In order to monitor enrollment, reconciliation will be performed between the number of patient-specific products shipped to the treating centers and the number of products reported in the registry databases. and the proportion of patients treated with liso-cel who are included in the registries will be calculated.

Based on discussions with the registry holders, CD19 expression data will not be available for all study patients and will have unique limitations. The CD19 expression data will not be available through the EBMT registry. For patients enrolled into the CIBMTR registry, only partial data will be available. The collection of CD19 expression data is not performed as part of the standard of

care at all sites (practice variations related to the availability of CD19 testing in routine clinical care). Furthermore, CD19 expression data may have to be captured retrospectively and may be reported incompletely in medical records. Where available, the process for requesting pathology reports will not follow any established standard mechanism, as CD19 expression is not part of CIBMTR's standard data collection forms and there is no notification on CIBMTR forms that a biopsy occurred. It may not always be feasible to obtain pathology reports from sites.

CD19 expression will only be available as binary variable, which will preclude analyzing the CD19 expression profile. Moreover, the binary variable may be based on different laboratory methods of measurement. Therefore, variability in the values of this binary variable between patients may not only result from variability in CD19 expression, but also from variability in the sensitivity of the different methods used.

With regards to timepoints at which CD19 expression is measured, CD19 expression data would preferably be collected at the time of liso-cel infusion, to avoid the data being influenced by intervening treatments. In practice, however, the timing of CD19 measurement will vary and in some cases, it might only be available at earlier timepoints (eg, at the time of diagnosis). Prior treatments may have an impact on CD19 expression. The further the measurement timepoint is from the liso-cel infusion timepoint, the higher the chances of a change in CD19 expression. This may make it difficult to detect any potential association between CD19 expression and liso-cel effectiveness.

9.10 Other Aspects

Not applicable.

10 PROTECTION OF HUMAN SUBJECTS

10.1 Good Pharmacoepidemiology and Pharmacovigilance Practices

This study will be conducted in accordance with good pharmacoepidemiology and pharmacovigilance practices (GVP).[71,72,73] The ENCePP checklist for study protocols is available in APPENDIX 2.

10.2 Ethics Committee Review

In accordance with local regulations, the MAH will be responsible for notifying and/or submitting the PASS protocol for approval to the relevant Ethics Committees, Independent Review Committees, Regulatory Authorities, and/or other local governance bodies in Europe, as applicable.

Given that this is an observational PASS, it does not give rise to additional risks for the safety of the patients.

10.3 Informed Consent

Data will only be part of the PASS if the patients (and parental/legal representative, when applicable) have given their voluntary informed consent to allow data to be provided to the EBMT or the CIBMTR and to be shared with competent health authorities, MAH, and other parties in line with the signed ICFs.

The ICF used to consent patients will be based upon the ICF templates of the EBMT and/or the CIBMTR, updated in line with the treatment center's standard practices/regulations to fulfill data protection and/or national requirements for informed consent, and allowing the registry holders to share pseudonymized patient-level data with third parties, including competent health authorities and the MAH, if the patient agrees. The registry holders will obtain the necessary approvals from Ethics Committees, Independent Review Committees, Regulatory Authorities, and/or other local governance bodies for conducting their registry and implementing their ICF within the participating treatment centers.

In case a patient treated with liso-cel in the postmarketing setting develops a secondary malignancy of suspected T cell origin, a separate ICF will be used for tumor tissue sample collection and liso-cel transgene testing outside the scope of this PASS.

11 COLLECTION AND REPORTING OF SELECTED ADVERSE EVENTS

Selected AEs associated with liso-cel treatment will be reported by HCPs at participating treatment centers using standard Registry CRFs per protocol and collected by the EBMT and/or the CIBMTR per standard registry procedures. The EBMT and/or the CIBMTR will extract data from CRFs and provide the MAH with a summary aggregate report and line listing every 3 months. The registry outputs will be periodically reported by the MAH to health authorities in an aggregate manner, according to applicable legislations, to support postmarketing liso-cel pharmacovigilance performed by both the MAH and the health authorities.

In addition to AEs collected by the Registries, participating HCPs will be encouraged to spontaneously report all ADRs directly to the MAH and/or to the applicable national health authorities in the EU (via spontaneous reporting tools).

In the event that a secondary malignancy of T cell origin is suspected, the MAH should be contacted to obtain instructions on the collection and transfer of a tumor tissue sample for testing in a separate process, outside of this PASS. In the postmarketing setting, the MAH will offer transgene assay service testing for all reported secondary malignancies of suspected T cell origin and other secondary malignancies where insertional oncogenesis is suspected where a sample is available, as a routine pharmacovigilance measure to ensure gathering the most information possible for clinical assessment of the reported spontaneous case.

Training on the HCP's responsibilities regarding reporting of adverse reactions, including secondary malignancies, will be provided by the MAH during the treatment center certification process and it will also be communicated by the EBMT and/or the CIBMTR. Health care professionals will be trained in AE severity grading by an MAH-retained third party and organ toxicities will be graded using the NCI CTCAE version 5.0 or higher.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In accordance with the milestones presented in Table 6-1, BMS is committed to submit to EMA interim reports at Year 5, Year 10, and Year 15 after European Commission decision or when the last patient is out of the registry-based study, and a final study report by Q4 2043.

BMS is additionally committed to submit to EMA summary aggregate safety reports and line listings via the PSUR. Study progress updates reports will also be integrated into the liso-cel PSURs, which will include any new potential safety concern/signal. The frequency of submission of PSURs will be determined by the European Union reference dates (EURD) list.

Information on study recruitment status will be included in study progress updates and interim reports.

This study is registered on the European Union electronic Register of Post-Authorisation Studies (EU PAS) register and the study protocol made available. Substantial amendments to the protocol and the final study report will also be made available in the register.

Results from the study may also be presented at congresses of hematology and/or oncology or submitted for publication to an appropriate scientific and medical journal.

13 REFERENCES

[1] Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, et al, (editors). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD. https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.

[2] Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang ML, Arnason JE, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020 Sep 19; 396(10254):839-52.

[3] Ekberg S, Smedby KE, Glimelius I, Nilsson-Ehle H, Goldkuhl C, Lewerin C, et al. Trends in the prevalence, incidence and survival of non-Hodgkin lymphoma subtypes during the 21st century - a Swedish lymphoma register study. Br J Haematol. 2020;189(6):1083-92.

[4] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): B-cell Lymphomas; V2 [Internet]; 2023 [cited 2023 Feb 8]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.

[5] Kanas G, Ge W, Quek RGW, Keeven K, Nersesyan K, Arnason, JE. Epidemiology of diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) in the United States and Western Europe: population-level projections for 2020-2025. Leuk Lymphoma. 2022 Jan;63(1):54-63.

[6] Kurz KS, Kalmbach S, Ott M, et al. Follicular Lymphoma in the 5th Edition of the WHO-Classification of Haematolymphoid Neoplasms-Updated Classification and New Biological Data. Cancers (Basel). 2023 Jan 27;15:785.

[7] Sant M, Allemani C, Tereneau C, De Angelis R, Capocaccia R, Visser O, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood. 2010;116(19):3724-34.

[8] Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-90.

[9] Riedell PA, Smith SM. Double hit and double expressors in lymphoma: Definition and treatment. Cancer. 2018;124(24):4622-32.

[10] Nguyen LN, Ha CS, Hess M, Romaguera JE, Manning JT, Cabanillas F, et al. The outcome of combined-modality treatments for stage I and II primary large B-cell lymphoma of the mediastinum. Int J Radiat Oncol Biol Phys. 2000;47(5):1281-5.

[11] Swerdlow SH, Campo E, Harris NL, et al., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon (France): IARC Press; 2017.

[12] Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022 Jul;36(7):1720-1748. Epub 2022 Jun 22. Erratum in: Leukemia. 2023 Sep;37:1944-51.

[13] Sant M, Allemani C, Tereneau C, De Angelis R, Capocaccia R, Visser O, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood. 2010;116(19):3724-34

[14] Epperla N, Hamadani M, Fenske TS, et al. Incidence and survival trends in mantle cell lymphoma. Br J Haematol 2018;181:703-6

[15] Jerkeman M, Ekberg S, Glimelius I, et al. Nationwide assessment of patient trajectories in mantle cell lymphoma: The Swedish MCLcomplete Project. HemaSphere. 2023;7(8):e928. doi:10.1097/hs9.0000000000000928

[16] Smedby KE, Hjalgrim H. Epidemiology and etiology of mantle cell lymphoma and other non‐Hodgkin lymphoma subtypes. Sem Cancer Biol. 2011;21(5):293‐298. doi:10.1016/j.semcancer.2011.09.010

[17] Tilly H, Morschhauser F, Sehn LH, Friedberg JW, Trněný M, Sharman JP, et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022;386(4):351-63.

[18] Wang Y, Farooq U, Link BK, Larson MC, King RL, Maurer MJ, et al. Late relapses in patients with diffuse large b-cell lymphoma treated with immunochemotherapy. J Clin Oncol. 2019;37(21):1819-27.

[19] Yescarta® [Summary of Product Characteristics]. Hoofddorp, The Netherlands: Kite Pharma EU B.V.; 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/yescarta-epar-product-information_en.pdf.

[20] Kymriah®. [Summary of Product Characteristics]. Dublin, Ireland: Novartis Europharm Limited; 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/kymriah-epar-product-information_en.pdf.

[21] Breyanzi®. [Summary of Product Characteristics] Dublin, Ireland: Bristol-Myers Squibb Pharma EEIG; 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/breyanzi-epar-product-information_en.pdf.

[22] Freedman A, Jacobsen E. Follicular lymphoma: 2020 update on diagnosis and management. Am J Hematol 2020;95(3):316-27.

[23] Kahl BS, Yang DT. Follicular lymphoma: evolving therapeutic strategies. Blood 2016;127(17):2055-63.

[24] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): B-cell Lymphomas; V5 [Internet]. 2023 [cited 07-Jul-2023]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.

[25] Casulo C, Dixon JG, Le-Rademacher J, et al. Validation of POD24 as a robust early clinical end point of poor survival in FL from 5225 patients on 13 clinical trials. Blood 2022;139(11):1684-93.

[26] Rodgers TD, Casulo C, Boissard F, Launonen A, Parreira J, Cartron G. Early relapse in first-line follicular lymphoma: a review of the clinical implications and available mitigation and management strategies. Oncol Ther 2021;9:329-46.

[27] Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: An analysis from the National LymphoCare Study. J Clin Oncol 2015;33(23):2516-22.

[28] Dreyling M, Ghielmini M, Rule S, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2021;32(3):298-308.

[29] Morschhauser F, Fowler NH, Feugier P, Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma. N Engl J Med. 2018 Sep 6;379(10):934-947.

[30] Cahill KE, Smith SM. Follicular Lymphoma: a focus on current and emerging therapies. Oncology (Williston Park) 2022;36(2):97-106.

[31] Rajamaki A, Sorigue M, Prusila REI, et al. Progression-free survival after front line, second line and third line in patients with follicular lymphoma treated in clinical practice. Acta Oncol. 2024 May 6;63:267-72.

[32] Gilead Sciences, Inc.; Withdrawal of Approval of Indications for Relapsed Follicular Lymphoma and Relapsed Small Lymphocytic Lymphoma," Federal Register, Vol. 87, No. 102, May 26, 2022. Available at: https://www.federalregister.gov/documents/2022/05/26/2022-11277/gilead-sciences-inc-withdrawal-of-approval-of-indications-for-relapsed-follicular-lymphoma-and#:~:text=The%20Food%20and%20Drug%20Administration%20(FDA%20or%20Agency)%20is%20announcing,.%2C%20333%20Lakeside%20Dr.%2C

[33] Secura Bio, Inc.; Withdrawal of Approval of Relapsed or Refractory Follicular Lymphoma Indication for Copiktra," Federal Register, Vol. 87, No. 71, April 13, 2022. Available at: https://www.federalregister.gov/documents/2022/04/13/2022-07931/secura-bio-inc-withdrawal-of-approval-of-relapsed-or-refractory-follicular-lymphoma-indication-for

[34] Bayer HealthCare Pharmaceuticals Inc.; Withdrawal of Approval of New Drug Application for Aliqopa," Federal Register, March 18, 2024. Available at: https://www.federalregister.gov/documents/2024/03/18/2024-05619/bayer-healthcare-pharmaceuticals-inc-withdrawal-of-approval-of-new-drug-application-for-aliqopa. Accessed on: 23-Mar-2025.

[35] Zydelig® (idelalisib). Summary of Product Charateristics - (eMC). Gilead Sciences Ireland UC; Revised Oct 2024. Available from URL: https://www.ema.europa.eu/en/medicines/human/EPAR/zydelig.

[36] Copiktra® (duvelisib). Summary of Product Charateristics - (eMC). Secura Bio Limited; Revised Jul 2022. Available from URL: https://www.ema.europa.eu/en/documents/product-information/copiktra-epar-product-information_en.pdf

[37] BRUKINSA® (zanubrutinib). Summary of Product Charateristics - (eMC). BeiGene Ireland Ltd; Revised Sept 2024. Available from URL: https://www.ema.europa.eu/en/documents/product-information/brukinsa-epar-product-information_en.pdf

[38] Tazverik® (tazmetostat). United States Prescribing Information. Cambridge, MA: Epizyme, Inc. 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/211723s005lbl.pdf

[39] FDA grants accelerated approval to mosunetuzumab-axgb for relapsed or refractory follicular lymphoma. Food and Drug Administration. December 23, 2022. Accessed on 23-Mar-2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mosunetuzumab-axgb-relapsed-or-refractory-follicular-lymphoma

[40] Mosunetuzumab Approved in Europe for Relapsed/Refractory Follicular Lymphoma. OncLive. June 8, 2022. Accessed on 23-Mar-2025. https://www.onclive.com/view/mosunetuzumab-approved-in-europe-for-relapsed-refractory-follicular-lymphoma

[41] FDA grants accelerated approval to epcoritamab-bysp for relapsed or refractory follicular lymphoma. Food and Drug Administration. June 26, 2024. Accessed on 23-Mar-2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-epcoritamab-bysp-relapsed-or-refractory-follicular-lymphoma

[42] Tepkinly® (epcortiamab). Summary of Product Charateristics. EMEA; 2024. Available from URL: https://www.ema.europa.eu/en/documents/product-information/copiktra-epar-product-information_en.pdf

[43] FDA grants accelerated approval to axicabtagene ciloleucel for relapsed or refractory follicular lymphoma. Food and Drug Administration. March 08, 2021. Accessed on 23-Mar-2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-axicabtagene-ciloleucel-relapsed-or-refractory-follicular-lymphoma

[44] FDA approves tisagenlecleucel for relapsed or refractory follicular lymphoma. Food and Drug Administration. May 31, 2022. Accessed on 23-Mar-2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tisagenlecleucel-relapsed-or-refractory-follicular-lymphoma#:~:text=On%20May%2027%2C%202022%2C%20the,more%20lines%20of%20systemic%20therapy

[45] June CH, Riddell SR, Schumacher TN. Adoptive cellular therapy: a race to the finish line. Sci Transl Med. 2015 Mar 25;7(280):280ps7.

[46] Avigan D. Vaccine therapy and adoptive immunotherapy in hematologic malignancies. Best Pract Res Clin Haematol. 2008 Sep;21(3):373-4.

[47] Nahas MR, Avigan D. Challenges in vaccine therapy in hematological malignancies and strategies to overcome them. Expert Opin Biol Ther. 2016 Sep;16(9):1093-104.

[48] Rosenblatt J, Glotzbecker B, Mills H, Vasir B, Tzachanis D, Levine JD, et al. PD-1 blockade by CT-011, anti-PD-1 antibody, enhances ex vivo T-cell responses to autologous dendritic cell/myeloma fusion vaccine. J Immunother. 2011 Jun;34(5):409-18.

[49] Kantoff PW, Schuetz TJ, Blumenstein BA, Glode LM, Bilhartz DL, Wyand M, et al. Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. J Clin Oncol. 2010 Mar 1;28(7):1099-105.

[50] Hamid O, Carvajal RD. Anti-programmed death-1 and anti-programmed death-ligand 1 antibodies in cancer therapy. Expert Opin Biol Ther. 2013 Jun;13(6):847-61.

[51] Page DB, Postow MA, Callahan MK, Wolchok JD. Checkpoint modulation in melanoma: an update on ipilimumab and future directions. Curr Oncol Rep. 2013 Oct;15(5):500-8.

[52] Rosenberg SA, Kochenderfer JN. Personalized cell transfer immunotherapy for B-cell malignancies and solid cancers. Mol Ther. 2011 Nov;19(11):1928-30.

[53] Sadelain M, Brentjens R, Riviere I. The basic principles of chimeric antigen receptor design. Cancer Discov. 2013 Apr;3(4)388-98.

[54] Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017 Dec 28;377(26):2531-44.

[55] Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019 Jan 3;380(1):45-56.

[56] Lee DW, Kochenderfer JN, Stetler-Stevenson M, Cui YK, Delbrook C, Feldman SA, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet. 2015 Feb 7;385(9967):517-28.

[57] Maude SL. Tisagenlecleucel in pediatric patients with acute lymphoblastic leukemia. Clin Adv Hematol Oncol. 2018 Oct;16(10):664-66.

[58] Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N Engl J Med. 2011 Aug 25;365(8):725-33.

[59] Siddiqi T, Soumerai JD, Wierda WG, Dubovsky JA, Gillenwater HH, Gong L, et al. Rapid MRD-negative responses in patients with relapsed/refractory CLL treated with liso-cel, a CD19-directed CAR T-cell product: preliminary results from Transcend CLL 004, a Phase 1/2 Study including patients with high-risk disease previously treated with ibrutinib. Blood. 2018;132 (Suppl 1):300.

[60] Raje NS, Berdeja JG, Lin Y, Munshi NC, DiCapua Siegel DS, Liedtke M, et al. bb2121 anti-BCMA CAR T-cell therapy in patients with relapsed/refractory multiple myeloma:

Updated results from a multicenter phase I study [abstract]. Presented at: The 54th Annual Meeting of the American Society of Clinical Oncology (ASCO). J Clin Oncol. 2018 May 20;36(15 suppl):8007-8007.

[61] Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-38.

[62] Gardner RA, Finney O, Annesley C, Brakke H, Summers C, Leger K, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood. 2017 Jun 22;129(25):3322-31.

[63] Hirayama AV, Turtle CJ. Toxicities of CD19 CAR-T cell immunotherapy. Am J Hematol. 2019 May;94(S1):S42-S49.

[64] Santomasso BD, Park JH, Salloum D, Riviere I, Flynn J, Mead E, et al. Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. Cancer Discov. 2018 Aug;8(8):958-71.

[65] Davila ML, Kloss CC, Gunset G, Sadelain M. CD19 CAR-targeted T cells induce long-term remission and B Cell Aplasia in an immunocompetent mouse model of B cell acute lymphoblastic leukemia. PLoS One. 2013 Apr 9;8(4):e61338.

[66] Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. N Engl J Med. 2013 Apr 18;368(16):1509-18.

[67] Morton LM, Curtis RE, Linet MS, Bluhm EC, Tucker MA, Caporaso N, et al. Second malignancy risks after non-Hodgkin's lymphoma and chronic lymphocytic leukemia: differences by lymphoma subtype. J Clin Oncol. 2010 Nov 20;28(33):4935-44.

[68] Maus MV, Levine BL. Chimeric Antigen Receptor T-Cell Therapy for the Community Oncologist. Oncologist. 2016 May;21(5):608-17.

[69] Kamdar M, Solomon SR, Arnason JE, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel (liso-cel), a CD19-directed chimeric antigen receptor (CAR) T cell therapy, versus standard of care (SOC) with salvage chemotherapy (CT) followed by autologous stem cell transplantation (ASCT) as second-line (2L) treatment in patients (Pts) with relapsed or refractory (R/R) large B-cell lymphoma (LBCL): results from the randomized Phase 3 Transform study. [abstract]. Presented at: The 63rd Annual Meeting of the American Society of Hematology (ASH) and Exposition. 2021; Atlanta, GA; USA: Abstract 91.

[70] Sehgal AR, Hildebrandt G, Ghosh N, Godwin JE, Wagner-Johnston ND, Hoda D, et al. Lisocabtagene maraleucel (liso-cel) for treatment of second-line (2L) transplant noneligible (TNE) relapsed/refractory (R/R) aggressive large B-cell non-Hodgkin lymphoma (NHL): Updated results from the PILOT study. J Clin Oncol. 2020;38(15):8040.

[71] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VI. EMA/873138/2011 Rev 2; 2017 Jul 28 [cited 2022 Jun 16]. Available from: URL: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-

pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf

[72] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VIII. EMA/813938/2011 Rev 3; 2017 Oct 9 [cited 2022 Jun 16]. Available from: URL: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf

[73] European Medicines Agency. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, EMA/95098/2010 Rev.9; 2021 [cited 2022 Jun 16]. Available from: URL: https://www.encepp.eu/standards_and_guidances/documents/1.ENCePPMethodsGuideRev.9.pdf

APPENDIX 1 LIST OF STAND-ALONE DOCUMENTS

None.

APPENDIX 2 ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Non-interventional, post-authorization safety study (PASS) of patients treated with commercially available liso-cel (lisocabtagene maraleucel) for large B-cell lymphomas

EU PAS Register® number: EUPAS103855
Study reference number (if applicable): JCAR017-BCM-005

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[1]	☒	☐	☐	6
1.1.3	Progress report(s)	☒	☐	☐	6
1.1.4	Interim report(s)	☒	☐	☐	6
1.1.5	Registration in the EU PAS Register®	☒	☐	☐	6
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)	☒	☐	☐	7.1
2.1.2	The objective(s) of the study?	☒	☐	☐	8
2.1.3	The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4	Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5	If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

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

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☒	☐	
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2/9.4/ 9.6
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.1
	4.2.2 Age and sex	☒	☐	☐	9.3
	4.2.3 Country of origin	☒	☐	☐	3/9.2
	4.2.4 Disease/indication	☒	☐	☐	9.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.1
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.1.2/ 9.2.1

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)	☐	☒	☐	
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?	☒	☐	☐	9.1/9.3
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.1/9.3
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
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)	☐	☐	☒	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

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)	☐	☐	☒	

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)	☒	☐	☐	9.2/9.4/ 9.6
	9.1.2	Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.2/9.3/ 9.4/9.6
	9.1.3	Covariates and other characteristics?	☐	☐	☒	
9.2	Does the protocol describe the information available from the data source(s) on:					
	9.2.1	Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.2/9.3/ 9.4/9.6
	9.2.2	Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.2/9.3/ 9.4/9.6
	9.2.3	Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	

Section 9: Data sources			**Yes**	**No**	**N/A**	**Section Number**
9.3	Is a coding system described for:					
	9.3.1	Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4/9.6 9.7.5.2/ 9.7.3
	9.3.2	Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4/9.6 9.7.5.2/ 9.7.3
	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)		☒	☐	☐	9.4/9.6

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7
10.4	Are stratified analyses included?	☐	☒	☐	
10.5	Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	9.9
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)	☒	☐	☐	9.4/9.6
11.2	Are methods of quality assurance described?	☒	☐	☐	9.8
11.3	Is there a system in place for independent review of study results?	☐	☐	☒	

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?	☒	☐	☐	9.9
	12.1.2 Information bias?	☒	☐	☐	9.9
	12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2	Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

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?	☒	☐	☐	3/9.2/10

Comments:

Section 14: Amendments and deviations		**Yes**	**No**	**N/A**	**Section Number**
14.1	Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results		**Yes**	**No**	**N/A**	**Section Number**
15.1	Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2	Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Main author of the protocol: