Title	Non-interventional, post-authorization safety study (PASS) of patients treated with commercially available liso-cel (lisocabtagene maraleucel) for relapsed/refractory diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and follicular lymphoma Grade 3B after 2 or more lines of systemic therapy in the postmarketing setting
Protocol Version Identifier	JCAR017-BCM-005 (also known as CA082-P21)
Date of Protocol Version	30-Aug-2022
EU PAS Register Number	To be confirmed
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 Objective • To characterize the incidence and severity 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 and 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: – by large B-cell lymphoma subtypes (eg, follicular lymphoma Grade 3B [FL3B], primary mediastinal B-cell lymphoma [PMBCL], diffuse large B-cell lymphoma [DLBCL] not otherwise specified [NOS], high-grade B-cell lymphoma [HGBCL]) – according to 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 – by 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
Country(-ies) of Study	United States (US); European countries; other countries may be included
Author	[redacted] Epidemiology/Hematology, Worldwide Patient Safety Bristol-Myers Squibb, Route de Perreux 1, 2017 Boudry Switzerland Telephone: [redacted] Email: [redacted]
MAH Contact Person	[redacted] Regulatory Affairs Bristol-Myers Squibb Pharma EEIG, Sanderson Road, Uxbridge, UB8 1DH United Kingdom Telephone: [redacted] Email: [redacted]

CONFIDENTIAL

This protocol is provided to you as an Investigator, potential Investigator, consultant or Registry holder for review by you, your staff, and ethics committee/institutional review board. The information contained in this document is regarded as confidential and, except to the extent necessary to obtain informed consent, may not be disclosed to another party unless such disclosure is required by law or regulations. Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

SIGNATURE PAGE

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Signature of Study Director

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Date Signed 01. September 2022

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ABC	activated B-cell-like
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
BMS	Bristol-Myers Squibb Company
CAR	chimeric antigen receptor
CAR T cell	chimeric antigen receptor T cell
CFR	Code of Federal Regulations
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CoO	cell of origin
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
[redacted]	
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Abbreviation	Definition
EU	European Union
EU PAS Register	European Union electronic Register of Post-Authorisation Studies
EURD	European Union Reference Dates
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
HDCT	high-dose chemotherapy
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
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
PMBCL	primary mediastinal large B-cell lymphoma

Abbreviation	Definition
PR	partial response
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-DHAP	rituximab, dexamethasone, cytarabine, and cisplatin
R-ICE	rituximab, ifosfamide, carboplatin, and etoposide
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 postauthorization 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 relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and follicular lymphoma Grade 3B (FL3B) after at least 2 prior therapies.

The main responsible parties are listed in Table 1.

Table 1: Responsible Parties

MAH:	Bristol-Myers Squibb Pharma EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867 Ireland
Main Author:	[redacted] Epidemiology/Hematology, Worldwide Patient Safety Bristol-Myers Squibb, Route de Perreux 1, 2017 Boudry Switzerland Telephone: [redacted] Email: [redacted]
Study Director:	[redacted] Epidemiology/Hematology, Worldwide Patient Safety Bristol-Myers Squibb, Route de Perreux 1, 2017 Boudry Switzerland Telephone: [redacted] Email: [redacted]
Principal Investigator:	Not applicable
EU QPPV:	[redacted] EEA QPPV, Worldwide Patient Safety Bristol-Myers Squibb GesmbH, Rivergate, Gate 1, Handelskai 92, 1200 Vienna Austria Email: [redacted]

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 relapsed/refractory diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and follicular lymphoma Grade 3B after 2 or more lines of systemic therapy in the postmarketing setting

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 objective

- To characterize the incidence and severity 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 and 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:
  - by large B-cell lymphoma subtypes (eg, follicular lymphoma Grade 3B [FL3B], primary mediastinal B-cell lymphoma [PMBCL], diffuse large B-cell lymphoma [DLBCL] not otherwise specified [NOS], high-grade B-cell lymphoma [HGBCL])
  - according to 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
  - by 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

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 relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and follicular lymphoma Grade 3B (FL3B) after 2 or more lines of systemic therapy treated with liso-cel therapy in the postmarketing setting, which includes patients treated with OOS product.

Data from at least [redacted] patients with a target of [redacted] patients – of which a minimum of [redacted] 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

Incidence and severity of selected adverse drug reactions (ADRs) reported post liso-cel infusion:

Primary Safety Endpoint(s)

- 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)

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. 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 above-mentioned eligibility criterion, 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 [redacted]:

- General identifiers (eg, patient code, treatment center identifier)
- [redacted]
- [redacted]
- 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)
- 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 [redacted] patients from registries is used based on pragmatic nonstatistical reasons, which is considered feasible within the estimated 5-year selection period. The study size is justified by providing precision estimates (see below).

To justify the sample size, precision estimates for example 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 (Noone, 2018). The incidences for CRS and neurotoxicity correspond to reported incidences of adverse events of special interest (AESIs) from Study 017001 [NCT 02631044] (Abramson, 2020).

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 [redacted] 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 [redacted] patients]	Clopper Pearson 95% CI upper
SEER 18 Regions, 2018	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
Abramson, 2020	Incidence of cytokine release syndrome ≥ Grade 3	269	6	0.022	0.013	0.036
	Incidence of neurotoxicity ≥ Grade 3	269	27	0.100	0.079	0.124

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 (Noone, 2018).

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: Quarter (Q)4 2022 (to be confirmed [TBC])[a]
- Start of data collection:[b] Q1 2023 (TBC)[a]
- Registration in the European Union electronic Register of Post-Authorization Studies (EU PAS Register): TBC
- Study Progress Updates: Per the Periodic safety update report (PSUR) cycle according to the EU reference dates (EURD) list
- Safety reports: Every 6 months (aligned with the reporting period of the PSUR).[c] Additional reports every 3 months if a new safety concern is identified
- Interim reports:[d] At year 5, 10, and 15 or when last patient is out of the registry-based study
- Date of Study Completion:[e] 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] Six-month safety reports will be provided with the PSUR submission (PSUR single assessment [PSUSA]) as determined by the EURD list.

[d] 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.

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

5 AMENDMENTS AND UPDATES

None.

6 MILESTONES

Milestones for this study are summarized in Table 2.

Table 2: 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	Q4 2022 (TBC)[a]
Start of data collection[b]	Q1 2023 (TBC)[a]
Registration in the EU PAS Register	TBC
Study Progress Updates	Per the PSUR cycle, according to the EURD list

Table 2: Milestones

Milestone	Date
Safety reports	Every 6 months (aligned with the reporting period of the PSUR).[c] Additional reports every 3 months if a new safety concern is identified
Interim reports[d]	At Year 5, Year 10, and Year 15 or when the last patient is out of the registry-based study
Date of Study Completion[e]	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] Six-month safety reports will be provided with the PSUR submission (PSUSA) as determined by the EURD list.

[d] 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.

[e] 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; PSUR, periodic safety update report; 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.

Non-Hodgkin lymphomas are classified according to the current World Health Organization (WHO) classification (Swerdlow, 2017) into immature lymphoid neoplasms, mature B-cell neoplasms, T cell and NK cell neoplasms, and posttransplant lymphoproliferative disorders.

Diffuse large B-cell lymphoma (DLBCL) is an aggressive type of mature B-cell lymphoma. It is the most common type of lymphoma, accounting for approximately 31% of all NHLs and 37% of

B-cell lymphomas worldwide (Hunt, 2008; Martelli, 2013). Between 2011 and 2012, the annual age adjusted incidence rates of DLBCL were between 3 to 4 per 100,000 persons in Europe and 6.9 per 100,000 persons in the United States (US) (Teras, 2016; Tilly, 2015).

Diffuse large B-cell lymphoma 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).

As the cyto-pathology definition of transformation is the apparition of a subset of large B cells, the group of transformed B-cell lymphomas can be considered with the de novo DLBCL as a group of "large B-cell lymphoma", in which some specific entities as primary mediastinal large B-cell lymphoma, and FL Grade 3B (FL3B) can also be included.

Molecular profiling by gene expression profiling (GEP) based on biologic similarity to normal stages of B-cell development (cell of origin [CoO]) helped to further divide DLBCL into germinal center B-cell-like (GCB), activated B-cell-like (ABC) tumors, and primary mediastinal large B-cell lymphoma (PMBCL), a distinct clinical entity (Lenz, 2008). Nevertheless, the prognostic and predictive value of the classification ABC versus GCB is still unclear and has currently no impact on the treatment choice in relapse setting.

The cases of aggressive B-cell lymphomas harboring the concurrent chromosomal rearrangements of c-MYC and the antiapoptotic oncogene BCL2, previously known as "double hit lymphoma", as well as the ones harboring a concurrent rearrangement of c-MYC and both antiapoptotic oncogenes BCL2 and BCL6, previously known as "triple hit lymphoma", are now specifically classified as high-grade B-cell lymphoma (HGBCL), with MYC and BCL2 and/or BCL6 rearrangements" (Swerdlow, 2016) and represent 7% to 10% of DLBCL (Rosenthal, 2017).

7.2.1 Current Treatment Options

Most patients with localized DLBCL can be cured with conventional combination immunochemotherapy, rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP) or combined-modality therapy, including radiotherapy (Tilly, 2015). Most patients with advanced-stage disease can be cured with a doxorubicin-based combination chemotherapy and rituximab (R-CHOP).

Overall, one third of patients will relapse after first-line treatment (Tilly, 2015). In addition, following the first-line treatment by the standard R-CHOP regimen, less than 10% of patients will experience refractoriness (Coiffier, 2002).

Patients with R/R DLBCL have a poor prognosis due to the lack of effective treatment options.

The standard of care for patients with R/R DLBCL after initial therapy is salvage therapy with platinum-based chemotherapy regimens (ie, rituximab, dexamethasone, cytarabine, and cisplatin [R-DHAP], rituximab, ifosfamide, carboplatin, and etoposide [R-ICE], or rituximab, gemcitabine, dexamethasone, and cisplatin [R-GDP]) if they are deemed to be eligible for high-dose chemotherapy (HDCT), followed by autologous hematopoietic stem cell

transplantation (ASCT) (Tilly, 2015). While approximately 50% to 60% of patients with R/R DLBCL remain sensitive to conventional second-line therapy, only roughly 30% will eventually proceed to ASCT (Gisselbrecht, 2010; Crump, 2014; Van Imhoff, 2017).

After ASCT in first relapse, the 48-month overall survival (OS) is 48% (Gisselbrecht, 2012). Patients who fail the first salvage regimen have a poor prognosis: median OS 4.4 months (Van Den Neste, 2016). In addition, approximatively one third of patients consolidated with ASCT in first line will eventually relapse. Despite third-line treatment, the prognostic outlook for those patients is poor as well, with a median OS of 10 months (Van Den Neste, 2017).

In addition, a substantial portion of patients are not eligible for transplantation (Gisselbrecht, 2018), as early as the first relapse, and have a lower survival rate. For those patients, regimens based on the ifosfamide-etoposide combination are generally preferred to the cytarabine-cisplatinum combination, with rituximab-bendamustine being a potential treatment option as well (Gisselbrecht, 2018).

There is no standard approach for the treatment of HGBCL. The R-CHOP regimen is mainly considered as not efficient enough. (Rosenthal, 2017). Chemoimmunotherapy refractoriness is problematic and relapse rates are high. Clinical trials are needed to establish a preferred therapeutic regimen and appropriate standard of care in first line as well as in the relapse setting. (Rosenthal, 2017). This is a disease area where the medical need is especially high (very poor OS of less than 12 months when treated with R-CHOP) (Camicia, 2015).

The R-CHOP regimen is still currently considered a good option to treat transformed FL in first line, especially anthracycline-naïve patients (Fischer, 2018). Autologous stem cell transplantation is considered as an option in the relapse setting. Clinical trials are strongly encouraged in this setting (Fischer, 2018).

The first-line treatment of PMBCL (immunochemotherapy anthracycline-based plus radiotherapy) produces a high level of cure. Nevertheless, the outcome of R/R PMBCL is considered very poor. Treatment strategies are similar to those used for other DLBCL, testing chemosensitivity with a salvage chemotherapy regimen (R-DHAP, R-ICE, others) followed by consolidation with HDCT-ASCT (Martelli, 2017).

In recent years, the treatment landscape has evolved with the approval of 2 chimeric antigen receptor T cell (CAR T cell) interventions (axicabtagene ciloleucel [Yescarta®] and tisagenlecleucel [Kymriah®]) and the salvage chemotherapy polatuzumab vedotin (Polivy®) in combination with bendamustine and rituximab in the US and the EU:

Axicabtagene ciloleucel was approved in the US in 2017 and in the EU in 2018 for the treatment of adult patients with R/R DLBCL and PMBCL after 2 or more lines of systemic therapy. Approval was based upon findings from the single-arm ZUMA-1 study (Locke, 2019).

Tisagenlecleucel received approval in the US and EU in 2018 for treatment of adult patients with R/R DLBCL after 2 or more lines of systemic therapy. Approval was based upon results from the single-arm JULIET study (Schuster, 2019c; Schuster, 2019).

Polatuzumab vedotin was granted conditional market approval in the US in 2019 and in the EU in January 2020 in combination with bendamustine and a rituximab product for the treatment of adult patients with R/R DLBCL who are not candidates for hematopoietic stem-cell transplant. Approval was based on data from 80 patients enrolled in the GO29365 randomized trial of polatuzumab vedotin with rituximab and bendamustine versus rituximab and bendamustine alone (Sehn, 2018; Sehn, 2020).

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 (June, 2015). Studies with tumor vaccines (Avigan, 2008; Nahas, 2016; Rosenblatt, 2011; Kantoff, 2010), immune checkpoint inhibitors (Hamid, 2013; Page, 2013), and tumor-infiltrating lymphocytes (Rosenberg, 2011) 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 (Sadelain, 2013).

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 (Schuster, 2019; Neelapu, 2017; Abramson, 2020), B-precursor acute lymphoblastic leukemia (ALL) (Maude, 2018; Lee, 2015), CLL (Porter, 2011; Siddiqi, 2018) and multiple myeloma (Raje, 2018).

Treatment with CAR T cell therapies showed significant clinical response. Initial studies demonstrated complete remissions of 63% of children with R/R ALL (Maude, 2018) and 40% to 45% of initial complete response in adults with R/R NHL (Schuster, 2019; Neelapu, 2017).

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 (Lee, 2019; Gardner, 2017). 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 (Hirayama, 2019).

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 (Santomasso, 2018). Rates and severity of neurotoxicities vary, with severe (Grade $\geq$ 3) manifestations observed in 12% to 28% of patients receiving CAR T cell therapy (Schuster, 2019; Abramson 2020; Neelapu, 2017).

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 (Lee, 2019).

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 (Davila, 2013; Grupp, 2013).

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 (Morton, 2010). 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 DLBCL patients 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 (Maus, 2016). 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) (Maus, 2016).

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 [redacted] 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. [redacted]

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 [redacted]. 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 (Abramson, 2020).

Data from Study 017001 in subjects with R/R large B-cell lymphoma, who have failed 2 or more lines of therapy, demonstrate that treatment with liso-cel results in encouraging efficacy outcomes. Among the 256 subjects in the DLBCL Efficacy Set, the overall response rate (ORR) was 73% and the complete response rate (CRR) was 53%. The median duration of response was not reached after a median follow-up of 12 months (95% CI 11.2 to 16.7 months); 60.4% of responders where still in response after 6 months (95% CI: 52.6 to 67.3), and 54.7% after 12 months (95% CI: 46.7 to 62.0). The OS in complete responders has not been reached with a median follow-up of 17.6 months and was 21.1 months (95% CI: 13.3 to NR) for the overall population.

In the safety population, among 269 subjects treated with liso-cel, CRS of any grade was reported in 113 (42%) subjects and 6 (2%) subjects had Grade ≥ 3 CRS. Investigator-identified neurotoxicity of any grade was reported in 80 (30%) subjects; 23 (9%) subjects had Grade 3 neurotoxicity and 4 (1%) subjects had Grade 4 neurotoxicity. No Grade 5 CRS or neurotoxicity occurred.

8 RESEARCH QUESTION AND OBJECTIVES

8.1 Research Question

This PASS is a noninterventional study of R/R DLBCL, PMBCL, FL3B after 2 or more lines of systemic therapy in 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 Objective

- To characterize the incidence and severity 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 and 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:
  - by large B-cell lymphoma subtypes (eg, FL3B, PMBCL, DLBCL NOS, HGBCL)
  - according to 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
  - by 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

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 R/R DLBCL, PMBCL, and FL3B after 2 or more lines of systemic therapy, treated with liso-cel therapy in the postmarketing setting, which includes patients treated with OOS product.

Data from at least [redacted] patients with a target of [redacted] patients – of which a minimum of [redacted] 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
  - tumor lysis syndrome (TLS)
  - infections
  - organ toxicities
  - others (eg, aggravated GVHD)

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)

9.2 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 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.

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. 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 3: 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 [redacted]	Product Name	Name of CAR T product
		[redacted]	
		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

Table 3: Variables

Classification	Category	Variable	Description
		Infused dose	Total number of cells or volume infused for each of the CD8+ and CD4+ cell components
		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

Table 3: Variables

Classification	Category	Variable	Description
		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
		Disease Status 4 Lymphoma Classification	Disease subtype (eg, FL3B, PMBCL, DLBCL NOS, HGBCL) 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
		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	ANC < 500/mm^3, platelet count < 20× 10^9/L

Table 3: Variables

Classification	Category	Variable	Description
		Prolonged Cytopenia 2 Recovery	Neutrophil and platelet recovery
		Hypogammaglobulinemia 1 Presence	Assessment and presence of hypogammaglobulinemia during follow-up
		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
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 1.

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

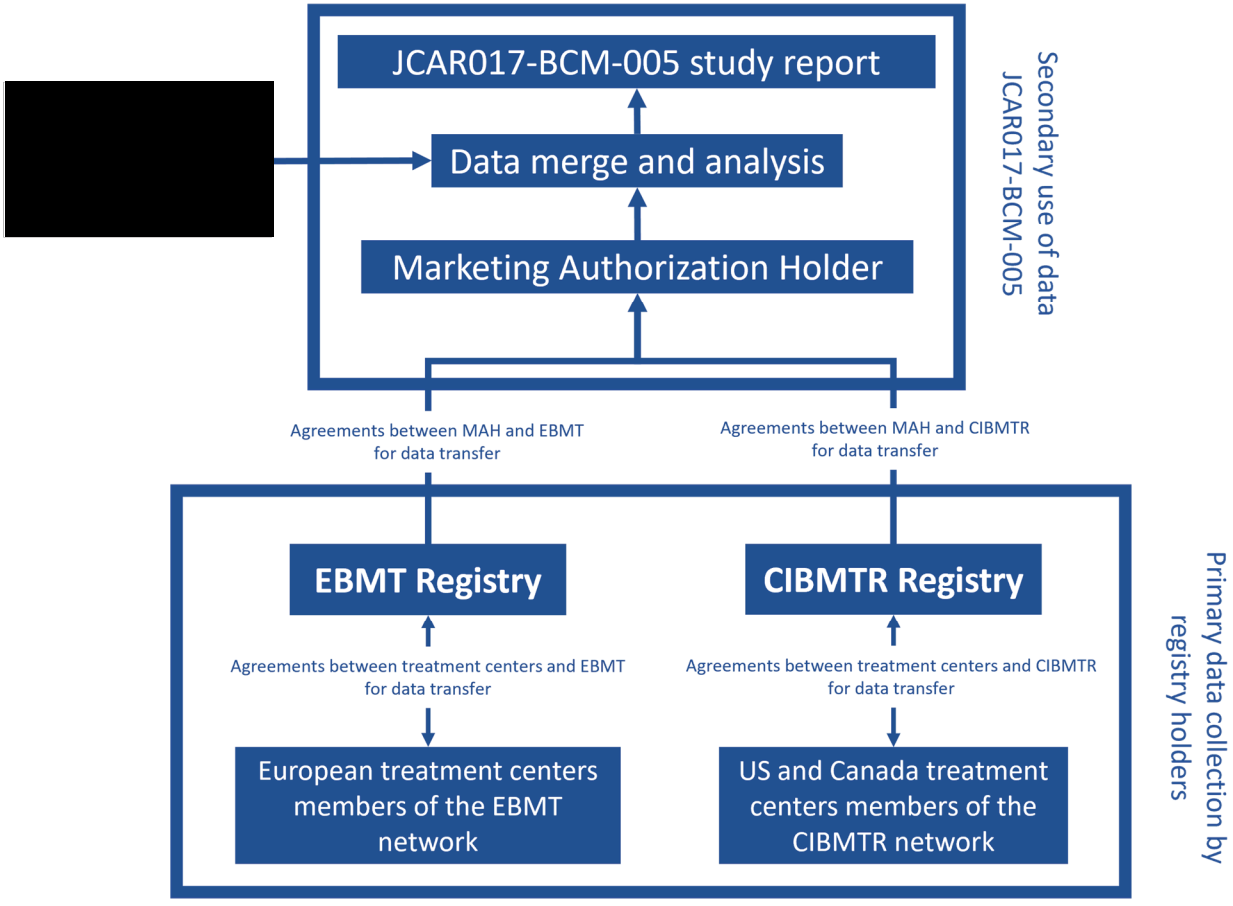

Diagram showing the current lines of communication between the MAH, registry holders, and treatment centers. The protocol provides the flexibility to include other data sources in the future, if available and required.

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 informed consent form (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 [redacted] patients from registries is used based on pragmatic nonstatistical reasons, which is considered feasible within the estimated 5-year selection period. The study size is justified by providing precision estimates (see below).

To justify the sample size, precision estimates for example 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 (Noone, 2018). The incidences for CRS and neurotoxicity correspond to reported incidences of adverse events of special interest (AESIs) from Study 017001 [NCT 02631044] (Abramson, 2020) (Table 4).

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 4: 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 [redacted] patients]	Clopper Pearson 95% CI upper
SEER 18 Regions, 2018	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
Abramson, 2020	Incidence of cytokine release syndrome ≥ Grade 3	269	6	0.022	0.013	0.036
	Incidence of neurotoxicity ≥ Grade 3	269	27	0.100	0.079	0.124

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 (Noone, 2018).

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 (CFR) 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.

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 defined subgroups.

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 above-mentioned eligibility criterion, 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:

- **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

- **Overall response rate (ORR):** ORR is the proportion of patients with a best overall response of complete response (CR) or partial response (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 computerized tomography (CT) and positron emission tomography (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 primary disease, whichever happens first. Patients who are alive and didn't experience disease progression, relapse or death due to primary disease before last contact date will be censored at that time, but no censoring will be done for additional treatment.
- **Progression-free survival (PFS):** 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 endpoint is 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
  - 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.

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.

9.8 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, sporadic 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.

The above-mentioned potential issue can lead to significant biasing effects on 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.

To minimize selection bias, treatment centers will be encouraged to include patients in the registries and will be requested to ask every patient treated with liso-cel to share data with the registry. 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 addition, in order to monitor the reporting, the study team will reconcile shipped products to each center participating in the study with the subsequent compliance of the patient and center with the study.

Additionally, as with every observational study, there will be unmeasured factors that can confound safety and effectiveness analyses. This PASS will attempt to collect accurate and complete data on all known critical confounders; however, residual confounding is always a possibility in any observational study analysis.

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) (EMA Guideline on GVP Module VI; EMA Guideline on GVP Module VIII; European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [ENCePP] Guide). 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 informed consent forms.

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 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.

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 2, 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. The frequency of submission of PSURs will be determined by the European Union reference dates (EURD) list. In case a new safety concern is identified, additional safety reports will be submitted to EMA every 3 months as stand-alone document.

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

This study will be 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.

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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 relapsed/refractory diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and follicular lymphoma Grade 3B after 2 or more lines of systemic therapy in the postmarketing setting

EU PAS Register® number: to be confirmed
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 collection1	☒	☐	☐	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:

[redacted]

Date:

Signature: *{See appended electronic signature page}*