LISOCABTAGENE MARALEUCEL, BMS-986387, BREYANZI®
RISK MANAGEMENT PLAN

Version: 9.1

Data-lock Point for this RMP: 04-Aug-2024

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LIST OF ABBREVIATIONS

Term	Definition
2L	second-line
3L+	third-line and greater
ADR	Adverse drug reaction
AE	Adverse event
allo	Allogeneic
ALT	Alanine aminotransferase
APVA	Additional Pharmacovigilance Activity(ies)
AR	Adverse reaction
ASCT	Autologous stem cell transplant
ASTCT	American Society for Transplantation and Cellular Therapy
ATA	Anti-therapeutic antibodies
ATC	Anatomical Therapeutic Chemical
B-ALL	B-cell acute lymphocytic leukaemia
BR	Bendamustine and rituximab
BTKi	Bruton Tyrosine Kinase inhibitor
CAR(s)	Chimeric antigen receptor(s)
CD	Cluster of differentiation
CDC	Centers for Disease Control
CI	Confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CNS	Central nervous system
COVID-19	Coronavirus Disease 2019
CR	Complete response
CRF	Case report form
CRP	C-reactive protein
CRR	Complete response rate
CRS	Complete release syndrome
CT	Compute tomography
ddPCR	droplet digital polymerase chain reaction
DL	Dose level
DLBCL	Diffuse large B-cell lymphoma
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DoR	Duration of response

Term	Definition
DSURs	Development safety update reports
EBMT	European Group for Blood and Marrow Transplantation
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
EGFRt	Truncated epidermal growth factor receptor
EMA	European Medicines Agency
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer - Quality of Life C30 questionnaire
EOS	End of study
EPAR	European Public Assessment Report
EQ-5D-5L	European Quality of Life-5 Dimension health state classifier to 5 Levels
ESMO	European Society for Medical Oncology
EU	European Union
EURD	European Union Reference Date
FACT-LymS	Functional Assessment of Cancer Therapy - Lymphoma “Additional concerns” subscale
FL	Follicular lymphoma
FL3B	Follicular lymphoma grade 3B
FSFV	First subject first visit
GMCT	Gene Modified Cell Therapy
GMP	Good manufacturing practices
GM T-cell	Gene modified T-cell
GvHD	Graft-versus-host disease
GVP	Good Pharmacovigilance Practices
HBV	Hepatitis B virus
HCP	Healthcare professional
HCV	Hepatitis C virus
HDCT	High dose chemotherapy
HEOR	Health economics and outcomes research
HGBCL	High grade B-cell lymphoma
HIV	Human immunodeficiency virus
HLH	Haemophagocytic lymphohistiocytosis
HMRN	Haematological Malignancy Research Network
hpf	High-power field

Term	Definition
HRQoL	Health-related quality of life
HRU	Hospital Resource Utilization
HSCT	Haematopoietic stem cell transplant
iiNT	Investigator-identified neurologic toxicity
IL	Interleukin
INN	International Non-proprietary Name
IPI	International Prognostic Index
IQR	Interquartile range
ISH	in-situ hybridization
IV	Intravenous
LBCL	Large B-cell lymphoma
LDC	Lymphodepleting chemotherapy
LDH	Lactate dehydrogenase
LSLV	Last subject last visit
LTFU	Long-term follow-up
LVV	Lentiviral Vector
MA	Marketing authorisation
MAA	Marketing Authorisation Application
mAb	Monoclonal antibody
MAS	Macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MAH	Marketing Authorisation Holder
MAS	Macrophage activation syndrome
MCL	Mantle cell lymphoma
MHC	Major histocompatibility complex
MOA	Mechanism of action
NHL	Non-Hodgkin lymphoma
NT	Neurologic toxicity
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PASS	Postauthorisation Safety Study
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PFS	Progression-free survival

Term	Definition
PFS-2	Progression-free survival on next line of treatment
PI	Product Information
PK	Pharmacokinetic
PL	Package leaflet
PMBCL	Primary mediastinal B-cell lymphoma
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PSUSA	PSUR single assessment
PT	Preferred term
PTCL	Peripheral T-cell lymphoma
PV	Pharmacovigilance
PY	Patient years
QA	Quality assurance
QC	Quality control
QoL	Quality of life
QP	Qualified person
QPPV	Qualified Person Responsible for Pharmacovigilance
qPCR	Quantitative polymerase chain reaction
R-CHOP	Rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone
RCL	Replication-competent lentivirus
RCR	Replication competent retroviruses
RfIC	Release for Infusion Certificate
RMP	Risk Management Plan
RNA	ribonucleic acid
R/R	Relapsed/refractory
RS	Relative survival
SAE	Serious adverse event
scFv	Single chain variable fragment
sCRS	Severe cytokine release syndrome
SD	Standard deviation
SEER	Surveillance Epidemiology and End Results
SIN	Self-inactivating
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query

Term	Definition
SOC	System Organ Class or Standard of care
SPD	Sum of products of the greatest diameters
SPM	Second primary malignancy
TCL	T-cell lymphoma
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TI	Transplant intended
TLS	Tumour lysis syndrome
TTO	Time to onset
UK	United Kingdom
US	United States
ULN	Upper limit of normal
WHO	World Health Organization

EU RMP FOR LISOCABTAGENE MARALEUCEL

RMP version to be assessed as part of this application:

Version Number: 9.1

Data-lock Point for this RMP: 04-Aug-2024

Date of Final Sign-off: 09-Oct-2025

Rationale for submitting an updated RMP:

Consolidation of EU RMP v7.0 (EMA/VR/0000265024: Type II variation for a new indication for Breyanzi as 3L treatment of adult patients with Relapsed/Refractory Mantle Cell Lymphoma based on study 017001-MCL Cohort.) and EU RMP v8.0 (EMA/VR/0000272242: Type II variation to propose a safety monitoring label update):

- Updated to include the indication for the treatment of adult patients with R/R MCL after at least 2 lines of systemic therapy, including a BTKi.
- Clinical exposure and safety data from Study 017001 (MCL Cohort) to support proposed indication.
- Updated to include epidemiology of MCL.
- Update the preventability section of CRS and NT in Part 2.7.3 to remove the patient monitoring timelines.
- Update to Objective of Patient Educational Programme in Part 5.2 and Annex 6

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part I Product Overview		
Product Details	Update to Indication(s) in the EEA	V.9.1 / pending
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	Update to include epidemiology of MCL	V9.1 / pending
SII Non-clinical part of the safety specification	N/A	V1.0 / 04-Apr-2022
SIII Clinical trial exposure	Updated to include safety data from Study 017001 (MCL Cohort)	V9.1 / pending
SIV Populations not studied in clinical trials	N/A	V5.1 / 30-Jan-2025
SV Post-authorisation experience	N/A	V6.1 / 21-Feb-2025
SVI Additional EU requirements for the safety specification	N/A	V1.0 / 04-Apr-2022

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
SVII Identified and potential risks	Updated to include safety data from Study 017001 (MCL Cohort) Update the preventability section of CRS and NT in Part 2.7.3 to remove the patient monitoring timelines.	V9.1 / pending
SVIII Summary of the safety concerns	N/A	V6.1 / 21-Feb-2025
Part III Pharmacovigilance Plan	N/A	V9.0 / 12-Aug-2025
Part IV Plan for post-authorisation efficacy studies	N/A	V6.1 / 21-Feb-2025
Part V Risk Minimisation Measures	Update to Objective of Patient Educational Programme	V9.1 / pending
Part VI Summary of the Risk Management Plan	Updated to align with changes made in the RMP	V9.1 / pending
Part VII Annexes		
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	N/A	V9.0 / 12-Aug-2025
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	N/A	V9.0 / 12-Aug-2025
ANNEX 4 Specific adverse drug reaction follow-up forms	N/A	V4.1 / 27-Jun-2024
ANNEX 5 Protocols for proposed and ongoing studies in RMP Part IV	N/A	V6.1 / 21-Feb-2025
ANNEX 6 Details of proposed additional risk minimisation activities	Update to Objective of Patient Educational Programme	V9.1 / pending
ANNEX 7 Other supporting data	N/A	V5.1 / 30-Jan-2025
ANNEX 8 Summary of changes to the risk management plan over time	Updated to include V9.1	V9.1 / pending

Other RMP versions under evaluation:

RMP Version Number	Submitted on	Procedure Number
None		

Details of the currently approved RMP:

Version number: 9.0

Approved with procedure: EMA/VR/0000288030

Date of approval: 12-Aug-2025

EU RMP Contact Person: PharmD. Roberta Di Menno Di Bucchianico, EU QPPV

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

1 PART 1: PRODUCT OVERVIEW

Table 1-1: Product Details

Active substance(s) (INN or common name)	Lisocabtagene maraleucel (liso-cel)[a]
Pharmacotherapeutic group(s) (ATC Code)	Anti-cancer, Immuno-oncology L01XL08 (Other antineoplastic agents)
Marketing Authorisation	Bristol-Myers Squibb Pharma EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	BREYANZI
Marketing authorisation procedure	Centralised
Brief description of the product	Liso-cel is a cluster of differentiation (CD)19-directed 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 an anti-CD19 chimeric antigen receptor (CAR) comprising a single chain variable fragment (scFv) binding domain derived from a murine CD19-specific monoclonal antibody (mAb; FMC63) and a portion of the 4-1BB co-stimulatory endodomain and CD3zeta (ζ) chain signalling domains and a non-functional truncated epidermal growth factor receptor (EGFRt).
Hyperlink to the Product Information	Refer to proposed Product Information (PI)
Indication(s) in the EEA	**Current:** Treatment of adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and follicular lymphoma grade 3B (FL3B) after two or more lines of systemic therapy. Treatment of adult patients with DLBCL, HGBCL, PMBCL, and FL3B who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy. Treatment of adult patients with R/R FL after two or more lines of systemic therapy. Treatment of adult patients with R/R MCL after at least 2 lines of systemic therapy, including a BTKi
Dosage in the EEA	**Current:** Liso-cel contains a target dose of 100×10^6 CAR+ viable T-cells (consisting of a target 1:1 ratio of CD8+ and CD4+ cell components) within a range of 44 - 120×10^6 CAR+ viable T-cells. Treatment is a single dose for infusion. A dose is suspended in one or more vials of each component. **Proposed:** Not applicable

Table 1-1: Product Details

Pharmaceutical form (s) and strength(s)	**Current:** CD8+ component Each vial contains lisocabtagene maraleucel at a batch-specific concentration of autologous T-cells genetically modified to express anti-CD19 chimeric antigen receptor (CAR+ viable T-cells). The medicinal product is packaged in one or more vials containing a cell dispersion of 5.1 - 322 × 10^6 CAR+ viable T-cells (1.1 - 70 × 10^6 CAR+ viable T-cells/mL) suspended in a cryopreservative solution. Each vial contains 4.6 mL of CD8+ cell component. CD4+ component Each vial contains lisocabtagene maraleucel at a batch-specific concentration of autologous T-cells genetically modified to express anti-CD19 chimeric antigen receptor (CAR+ viable T-cells). The medicinal product is packaged in one or more vials containing a cell dispersion of 5.1 - 322 × 10^6 CAR+ viable T-cells (1.1 - 70 × 10^6 CAR+ viable T-cells/mL) suspended in a cryopreservative solution. Each vial contains 4.6 mL of CD4+ cell component. More than one vial of each of the CD8+ cell component and/or CD4+ cell component may be needed to achieve the dose of liso-cel. The total volume to be dosed and the number of vials required may differ for each cell component. **Proposed:** Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

[a] "Lisocabtagene maraleucel (liso-cel, JCAR017)" will be referred to throughout this RMP as liso-cel, except where "JCAR017" is used in clinical study protocol titles.

2 PART II: SAFETY SPECIFICATION

2.1 Epidemiology of the Indication(s) and Target Population(s)

2.1.1 Diffuse Large B-cell Lymphoma

Table 2.1.1-1: Epidemiology of Patients with Diffuse Large B-cell Lymphoma

Diffuse Large B-cell Lymphoma	
Incidence	• The European Standardised incidence of DLBCL per 100,000 person-years - using population-based data from France in 2018 - was 6.5 (95% CI: 6.1-7.0) in men and 4.4 (95% CI: 4.1-4.7) in women.[1] • The cumulative incidence of R/R DLBCL among curatively treated patients with DLBCL was 18.9% (95% CI: 17.7-20.2) and 23.1% (95% CI: 21.7-24.6), at

Table 2.1.1-1: Epidemiology of Patients with Diffuse Large B-cell Lymphoma

Diffuse Large B-cell Lymphoma	
	2-years and 5-years after diagnosis, respectively, in a population-based Swedish study.[2] • There is scarce recent evidence of increasing trends in incidence of DLBCL in Europe. In Sweden the incidence of DLBCL increased by 2.2% annually between 2000 and 2016.[3] Whereas, in France, incidence rates for DLBCL increased annually by 1.2% in women from 2005-2012.[1] • Incidence data from 1995 onward from cancer registries in the United States (US) that participate in the Centers for Disease Control (CDC) and Prevention National Program of Cancer Registries (Surveillance Epidemiology and End Results; SEER) program estimated the 2011 to 2012 age-adjusted incidence rate for DLBCL to be 6.9 per 100,000 in the United States (US).[4] Over the period 2016-2020, the crude incidence rate of DLBCL per 100,000 person-years (PY) was 8.02 overall (7.01 in females and 9.05 in males).[5]
Prevalence	• In Sweden, the 5-year prevalence of DLBCL increased by 66%, from 2004 to 2016.[3] The 5-year prevalence was estimated at 28.4 (27.2-29.6) per 100,000 and the annual increase of the 5-year prevalence was 1.039 (1.033, 1.045). Assuming the same increase is maintained from 2016 to 2020, the 5-year prevalence in 2020 would be 32.5 (95% CI: 31.2-34.0) per 100,000. • In Belgium, the number of 5-year and 10-year prevalent cases alive in 2018 was reported from the Belgian Cancer Registry (2021): namely, 2,674 5-year cases (2014-2018) and 4,495 10-year cases (2009-2018). Using the 2018 Belgian population (11,427,054),[6] the corresponding 5-year and 10-year prevalence per 100,000 in 2018 is 23.4 and 39.0, respectively.
Demographics of the population: age, gender, racial and/or ethnic origin	• The incidence of DLBCL is known to increase with age. The median age at diagnosis is approximately 70 years.[7,8] • DLBCL is slightly more common in males than females.[7,8,9]
Risk factors for the disease	• A family history of lymphoma, autoimmune disease, human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) seropositivity, a high body mass as a young adult and some occupational exposures have been identified as risk factors for or predisposing to DLBCL.[10,11,12]
Main treatment options	• Most patients with localised DLBCL can be cured with conventional combination immunochemo- or combined-modality therapy.[11] For patients with advanced-stage disease, approximately 60% of patients can be cured with anthracycline-based combination chemotherapy and rituximab (eg, R-CHOP). • Treatment strategies generally depend on the individual risk profile, including the IPI, and the patient's comorbidities, as indicated in the recommendations of the European Society for Medical Oncology (ESMO).[11,13] • According to the ESMO recommendations 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, rituximab, ifosfamide, carboplatin and etoposide, or rituximab, gemcitabine, dexamethasone, and cisplatin) if they are deemed to be eligible for high dose chemotherapy (HDCT) and autologous stem cell transplant

Table 2.1.1-1: Epidemiology of Patients with Diffuse Large B-cell Lymphoma

Diffuse Large B-cell Lymphoma	
	(ASCT).[11] Patients responding to second line salvage therapy (ie, those with chemo-sensitive disease) might proceed to HDCT and ASCT to consolidate their response. • Allogeneic transplantation with a sibling or matched unrelated donor may be considered in highly selected patients with refractory disease, early relapse or relapse after ASCT.[14] • For patients not suitable for HDCT, treatment is rather palliative and may use the same or other salvage regimens such as rituximab, gemcitabine, oxaliplatin.[15] Pixantrone received a conditional Marketing Authorisation (MA) in the EU in 2012 for the treatment of adults with multiple R/R aggressive non-Hodgkin lymphoma (NHL) and is included in ESMO DLCBL treatment guidelines.[11] • Since August 2018, the CD19-directed CAR T therapies axicabtagene ciloleucel (Yescarta®) and tisagenlecleucel (Kymriah®) are approved for treatment of patients with R/R DLBCL after at least two lines of prior therapy. In addition, a conditional MA was granted in the EU in January 2020 for polatuzumab vedotin (Polivy®) in combination with BR for the treatment of adults R/R DLBCL, who are not candidates for haematopoietic stem cell transplant (HSCT).
Mortality and morbidity (natural history)	• Although DLBCL is associated with a median overall survival (OS) of less than 1 year in untreated patients, newly diagnosed disease is commonly curable (approximately 60% of patients) with first-line immunochemotherapy (R-CHOP).[16,17] • Using data from the United Kingdom (UK)'s HMRN from 2004 to 2016, the 5-year relative survival (RS, ie the ratio of the observed survival of patients with the disease at the end of a defined time period to the survival in the general population of the same age and sex at the end of the same period) was estimated at 59.8% (95% CI: 57.9-61.6).[18] • Based on the US SEER registries, the 5-year RS modestly improved from 61% in 2002-2007 to 64% in 2008-2013.[19] • In another population-based study in the Netherlands, the 5-year RS rates for patients with DLBCL under 65 years of age increased remarkably by 18%, from 57% in the period 1989 through 1993 to 75% in the period 2005 through 2010. Relative survival for patients aged 65 to 74 years rose by 22%, from 40% in the period 1989 through 1993 to 62% in the period 2005 through 2010. For patients over 75 years of age, survival increased by 13%, from 28% in the period 1989 through 1993 to 41% in the period 2005 through 2010.[8] • Although relapse rates have decreased, one-third of patients will have primary refractory disease or develop a subsequent relapse and consequently a dramatic worsening of the prognosis.[20,21] • While in clinical trials approximately half of patients who progress during 1L immunochemotherapy or within 12 months after a CR to 1L therapy are theoretically candidates for HSCT, about 30% to 40% of patients will ultimately undergo HSCT. In contrast, in a real-world nationwide population-based study in Sweden only 18% of the patients with R/R DLBCL proceed to ASCT.[22] Only a quarter of all 2L R/R LBCL clinical trial patients who are intended for HSCT

Table 2.1.1-1: Epidemiology of Patients with Diffuse Large B-cell Lymphoma

Diffuse Large B-cell Lymphoma	
	achieve durable remission, with 3- and 4-year PFS rates in the range of 30% to 40% and 3- and 4-year OS rates in the range of 40% to 50%.[23,24,25] • For patients failing second line salvage treatments, prognosis is very poor with a median survival of only 3 to 4 months.[26,27]
Important co-morbidities	Among 3905 adult patients diagnosed with DLBCL (median age at diagnosis: 70 years, range: 18 to 105 years) through the Swedish Lymphoma Register, the most common comorbidities of DLBCL patients were:[28] • Solid cancer • Metastatic cancer • Cardiovascular disease • Diabetes • Cerebrovascular disease • Chronic pulmonary disease • Peptic ulcer disease • Rheumatologic disease • Peripheral vascular disease • Liver disease • Renal disease • Dementia • Psychiatric disorders

2.1.2 Primary Mediastinal B-cell Lymphoma

Table 2.1.2-1: Epidemiology of Patients with Primary Mediastinal Large B-cell Lymphoma

Primary Mediastinal Large B-cell Lymphoma	
Incidence and Prevalence	• PMBCL accounts for 2% to 3% of B-cell NHL and 10% of large B-cell lymphomas.[29,30] • In the UK, the annual incidence rate was 0.2 per 100,000 over 2010-2016.[31]
Demographics of the population: age, gender, racial and/or ethnic origin	• PMBCL occurs predominantly during the third and fourth decades of life and is more common in women. It is uniformly distributed around the world.[32] • Females had significantly higher incidence than males (ratio 3:1). However, this difference was apparent for the white population only. A peak of incidence was shown at 30 to 39 years for white, black, and other groups.[33]
Risk factors for the disease	• Aside from female gender, PMBCL has no known risk factors.
Main treatment options	• Standard frontline therapy for PMBCL consists of immuno-chemotherapy [34] such as R-CHOP; etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone and bleomycin; methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisolone and bleomycin; or more intensive chemotherapy regimens such as dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin and rituximab. • Salvage treatment strategies for R/R patients are similar to DLBCL and include reinduction with non-cross-resistant agents followed by consolidation with HDCT and ASCT in patients with chemosensitive disease.
Mortality and morbidity (natural history)	• Patients with PMBCL often present with cough, dyspnoea, chest pain, and superior vena cava syndrome. Lactate dehydrogenase is elevated in half to two-thirds of patients. At diagnosis most patients (70 to 80% have stage I or II disease. Initial presentation can be nodal or extranodal; however, relapse is frequently extranodal and may involve liver, gastrointestinal tract, kidneys, and ovaries. Bone marrow involvement is uncommon and observed in 2% of cases.[35,32] • 10% to 30% PMBCL patients have R/R disease and require salvage therapies, which do not offer satisfactory outcomes.[36] • Relapse usually occurs within 12 months, is more likely to be widespread and can involve the CNS. Late relapses are very uncommon. Once R/R, the 5-year PFS is around 27%.[37] • In a Swedish population-based study of patients registered with PMBCL in 2007-2018, with an 8-year median follow-up for patients alive at the end of the study period, 14% of the patients died.[38]
Important co-morbidities	Among 148 PMBCL patients identified from Optum's Clinformatics Data Mart Databases, the most common baseline comorbidities were:[39] • Hypertension • Chronic pulmonary disease • Diabetes • Valvular disease

Table 2.1.2-1: Epidemiology of Patients with Primary Mediastinal Large B-cell Lymphoma

Primary Mediastinal Large B-cell Lymphoma	
	• Depressive disorders

2.1.3 Follicular Lymphoma

Table 2.1.3-1: Epidemiology of Patients with Follicular Lymphoma

Follicular Lymphoma	
Incidence	• FL is the second most common form of indolent lymphoma in the US and Europe, and accounts for about 10% to 20% of NHL.[40] Approximately 80% to 90% of FL are FL Grade 1 or 2 (FL 1/2). From the remaining 10% to 20%, it is estimated that approximately one quarter are FL3B.[41] FL3B comprises only 1% of NHL cases.[29,42] • In France, the crude incidence per 100,000 (95%CI) in 2018 was 5.3 (4.8-5.8) in males and 4.2 (3.7-4.7) in females; the corresponding rates standardized to the European population were 4.1 (3.8-4.5) and 2.9 (2.6-3.3).[43] The world-standardized incidence increased on average by 3.0% per year in males and by 0.8% per year in females from 2010 to 2018. • In Sweden, the age-standardized incidence rate (standardized to 2019 Swedish population) was 3.67 per 100,000 in men and 3.39 in women.[44] • Crude incidence rate of FL in the US was 3.59 per 100,000 person years in the period 2016-2020.[5] In the UK, the crude annual incidence rate from the HMRN during 2010 through 2019 was 3.6 per 100,000.[45] • Incidence age-standardized incidence rates decreased by 1.2% per year over 2012-2021.[46]
Prevalence	• The 5-, and 10-year prevalences of FL per 100,000 estimated from UK HMRN database are 16.9 and 27.7, respectively.[45]
Demographics of the population: age, gender, racial and/or ethnic origin	• The median age at diagnosis is 64 in the US and 67 in the UK.[5,45] • In the US, Caucasians have the highest incidence rates and non-Hispanic Blacks the lowest.[5]
Risk factors for the disease	• Risk factors for FL are poorly understood. Other than age, gender and ethnicity, environmental and occupational exposure to benzenes and pesticides have been implicated, but a clear association has not been established. Lifestyle factors such as smoking, alcohol use, and obesity have also been implicated in various studies, but conflicting results have not established a clear association with increased risk of FL.[47] • Approximately 90% of patients with FL have a translocation of chromosome 14q32 and 18q21 which results in the overexpression of the BCL2-protein, a member of a family of proteins that block apoptosis. However, t(14;18) is not infrequently detected in lymphocytes in peripheral blood of healthy individuals. Overt FL has several additional gene alterations involved in epigenetic

Table 2.1.3-1: Epidemiology of Patients with Follicular Lymphoma

Follicular Lymphoma	
	modification, JAK/STAT signaling, immune modulation, and NF-κB signaling, indicating multi-step lymphomagenesis in FL.[48] • Factors for transformation to DLBCL have been controversial. Clinical risk factors include elevated beta-2-microblobulin levels, high IPI, high FL IPI score, and advanced stage (III and IV). Some studies suggest that time and treatment approach (watch and wait as first-line therapy versus treatment with rituximab) are possible risk factors for transformation. However, due to the variable follow-up time, inclusion criteria and treatments, findings in various studies have been inconsistent.[40]
Main treatment options	• Current guidelines recommend treating FL3B according to the DLBCL treatment algorithm.[30, 49 , 50] These patients are generally treated with an anthracycline-based chemotherapy combined with rituximab (eg, R-CHOP) and have a similar prognosis to that of de novo DLBCL. There is no formal standard of care for second-line treatment. Beside rituximab, alone or in combinations with lenalidomide, immunochemotherapy remains the principal recommended option.[51] • Grade 1 to grade 3A FL are termed classic FL in the 2022 WHO classification. In early stage (I/II) classic FL, radiation therapy is generally the treatment of choice and results in a median survival of approximately 19 years.[52] Treatment may also include anti-CD20 monoclonal antibody with or without chemotherapy (NCCN). Most patients with FL have advanced stage disease at diagnosis. Patients with advanced stage FL do not require immediate treatment unless they have symptomatic nodal disease, compromised end organ function, B symptoms; symptomatic extranodal disease, or cytopenias.[52] Treatment options in 1L include an anti-CD20 monoclonal antibody with or without chemotherapy[53] 2L therapeutic options are similar to 1L.[52,53] For highly selected R/R patients, both ESMO [54] and NCCN[53] guidelines state that treatment may also include HSCT. In patients who experienced long remission after frontline therapy, guidelines suggest that the initial 1L regimen may be repeated in 2L therapy.[53,54] After 2 lines of therapy, treatment options for R/R FL patients are limited.
Mortality and morbidity (natural history)	• The natural history of FL is indolent in nature, with most patients developing several relapses over their lifetime. As the disease progresses, subsequent relapses can become progressively aggressive and refractory, and some cases may transform into aggressive lymphoma.[55] FL Grade 3B, however, is regarded as an aggressive lymphoma. Clinical behaviour of FL Grade 3B is very similar to DLBCL. • According to the World Health Organization (WHO) criteria, FL tumours are histologically divided into three grades: grade 1 (< 5 centroblasts per high-power field [hpf]), Grade 2 (6 to 15 centroblasts/hpf), and Grade 3 (> 15 centroblasts/hpf). Grade 3 is further subdivided into Grade 3A (centrocytes still present) and Grade 3B (the follicles consist almost entirely of centroblasts). Grades 1 through 3A are considered to be indolent and incurable, whereas Grade 3B is considered an aggressive but curable disease similar to DLBCL.[47]

Table 2.1.3-1: Epidemiology of Patients with Follicular Lymphoma

Follicular Lymphoma	
	• The overwhelming majority of FL patients have advanced stage disease at diagnosis, whereas less than 10% of patients have Stage 1/2 disease at diagnosis. Studies have reported that 10% to 70% of patients transform to DLBCL over time, with an estimated risk of 2% per year.[56] • In the Netherlands, 5-year RS in patients diagnosed with FL between 2000 and 2017 was 85% (95% CI: 84-87%).[57] • Five-year RS for patients with FL ranged from 81% in black males to 87% in white females in the US.[4]
Important co-morbidities	Comorbidities associated with FL are usually due to the advancing age of the patient. Such patients are more likely to develop cardiovascular, neurological, kidney injuries and complications as well as mucositis.[58]

2.1.4 Mantle Cell Lymphoma

Table 2.1.4-1: Epidemiology of Patients with Mantle Cell Lymphoma

MCL	
Incidence and Prevalence	• In Germany, MCL represents 4% and 7% of the incident NHL cases in men and women, respectively;[59] in the Swedish population it represented 5.5% of the lymphomas.[44] • In the US 2.6% of the NHL were MCL over the period 2017-2021[60] • The crude incidence rate per 100,000 of MCL in France was 2.1 in men and 0.6 in women in 2018[43] in the UK it was 0.9 overall, 1.3 in men and 0.5 in women over the period 2010-2019.[61] • In the US the crude annual incidence rates (2017-2021) were 1.0 overall, 1.4 in men and 0.5 in women.[60] • MCL incidence increased on average by 2.2% per year in men over the period 2003-2018, whereas it remained stable in women.[43] • The 5-year prevalence per 100,000 in the UK is estimated at 2.9;[61] and it is 3.22 in the US.[60] The overall 2013 prevalence in Belgium was estimated at least at 3.62 per 100,000.[62]
Demographics of the population: age, gender, racial and/or ethnic origin	• The median age at diagnosis was 72.2 years in the UK,[61] Similarly, in France it was 70 years in men and 73 years in women;[43] and in Sweden it was 71 in men and 72 in women. [44] • In the US, MCL incidence rate per 100,000 was highest among non-Hispanic whites (1.4) and lowest among non-Hispanic Blacks (0.3).[60]
Risk factors for the disease	• As noted above, the incidence of MCL is 2.6- to 3.5-fold higher in men than in women.

Table 2.1.4-1: Epidemiology of Patients with Mantle Cell Lymphoma

MCL	
	• Factors that are important for the development of other lymphomas, such as familial risk, immunosuppression, other immune disorders, chemical and occupational exposures, and infectious agents, have not been convincingly identified as predisposing factors for mantle-cell lymphoma, with the possible exception of family history.[81]
Main treatment options	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.[63](Kumar, 2019) Per ESMO guidelines (Dreyling, 2017),[64] the preferred option after failure of 1L treatment in MCL is treatment with ibrutinib, a covalent BTKi, which was initially approved in the EU on the basis of a single-arm Phase 2 study and subsequently confirmed in a randomized study showing PFS superiority to temsirolimus.[65,66] (Wang, 2013; Imbruvica, 2024) There is no single standard-of-care treatment for R/R MCL in the post-BTKi setting, the optimal approach/sequence to treat R/R MCL is yet to be defined and there is lack of data comparing the available treatment options in a randomized controlled fashion. The treatment choice for R/R MCL patients is influenced by age, perfomance status, comorbidities, and prior therapy.[64,67] The approved treatment options available in EU include temsirolimus, lenalidomide and bortezomib.[68,69,70] Both temsirolimus and lenalidomide are approved for R/R MCL but show limited efficacy (ORR 22.2% to 40.0%, CR rate 3% to 4.7%).[68, 69, 71] Chemoimmunotherapy regimens (rituximab-bendamustine ± cytarabine) are also additional options that have been associated with high response rates (up to 83%) but with a limitation of associated toxicity resulting in dose reduction.[72,73] Recently, 2 additional agents have been granted conditional marketing authorization in EU for the treatment of R/R MCL in the post-BTKi setting: o Brexucabtagene autoleucel (KTE-X19; Tecartus®; hereafer referred to as brexu-cel), an autologous CD19-directed CAR T-cell therapy for the treatment of R/R MCL after ≥ 2 lines of systemic therapy, including a BTKi.[74] o Pirtobrutinib (Jaypirca®), a non-covalent BTKi for the treatment of adults with R/R MCL after ≥ 2 lines of systemic therapy, including a BTKi.[75] Patients with R/R MCL progressing after 2 or more lines of therapy, specifically after covalent BTKi treatment, have limited therapeutic options and outcomes. Development of resistance or intolerance to covalent BTKi therapies is common.[76] In addition, toxicities from long-term use of BTKi therapies may not be tolerable for all patients, thus limiting their prolonged use for the treatment of R/R MCL.[77] The majority of patients with R/R MCL die of their disease post BTKi treatment. An SLR was performed to assess the clinical efficacy and safety of 3L+ treatment options for adult R/R MCL patients who had been previously exposed to a BTKi.[78]

Table 2.1.4-1: Epidemiology of Patients with Mantle Cell Lymphoma

MCL	
	The SLR reviewed studies published up to 7-Aug-2024 and identified 72 publications representing 19 unique studies. These studies evaluated a range of treatments, including the rituximab-bendamustine combination regimen, lenalidomide-based regimens, and various mixed treatment approaches (e.g., cohorts including different proportions of chemotherapy ± anti-CD20 agents, covalent BTKi-based regimens, bortezomib-based regimens, lenalidomide-based regimens, venetoclax, radiotherapy, etc.), non-covalent BTKi (pirtobrutinib), and CAR T-cell therapies such as brexu-cel and liso-cel. Of the 19 studies, 10 (53%) studies focused on non-CAR T-cell therapies and 9 (47%) investigated CAR T-cell therapies. The results from this SLR underscore the limited treatment options available for the 3L+ R/R MCL patients in the post-BTKi setting. Rituximab-bendamustine combination therapies and lenalidomide-based therapies are associated with suboptimal clinical outcomes. While newer treatments, such as brexu-cel and pirtobrutinib, have shown improved efficacy, there are associated limitations: the rates of toxicity with brexu-cel may limit its wider suitability in the R/R MCL patient population that presents with advanced median age and comorbidities, and pirtobrutinib is associated with the burden of continuous daily administration and toxicities, which could recur during treatment leading to dose reduction and permanent discontinuation. There is a clear unmet need for additional therapeutic options for R/R MCL patients who have previously received BTKi treatment in the 3L+ setting.
Mortality and morbidity (natural history)	• Five-year overall survival is 48% in France,[43] and 36% in the UK;[79] and 51% in the US.[60] • The clinical presentation differs among the two major subtypes of MCL: nodal MCL and leukemic, non-nodal MCL • Nodal MCL accounts for at least three-quarters of cases of MCL. Most patients present with lymphadenopathy, but nodal MCL may also manifest splenomegaly and/or involve extranodal sites. Lymphadenopathy may be relatively asymptomatic (eg, with smoldering MCL), or it can be more generalized and progressive. Involvement that is limited to a single lymph node region (ie, stage I) is rare. • Extranodal sites are often involved by MCL, but isolated or predominant extranodal presentation is uncommon[80] and more than 80% have stage III or IV disease at diagnosis.[81] About 30% of patients have fevers, sweats, or weight loss, but more patients report fatigue. Bulky lymphadenopathy (i.e., masses ≥10 cm in the greatest diameter) is seen in approximately 25% of patients, and less than half of patients have an elevated lactate dehydrogenase level. Central nervous system involvement, which is rare at the initial presentation, is associated with a very short survival. • Examples of extranodal involvement by MCL include the Gastrointestinal tract, upper airways and Waldeyer ring, ocular adnexa, oral cavity and salivary glands among others. GI involvement is very common, and it can involve any region of the GI tract. Patients may present with prominent GI symptoms, but others are asymptomatic.[80] In some instances, GI tract involvement takes the form of symptomatic intestinal polyps (so-called multiple lymphomatous polyposis).

Table 2.1.4-1: Epidemiology of Patients with Mantle Cell Lymphoma

MCL	
	• Mantle-cell lymphoma has a number of other characteristic presentations. One of these involves circulating lymphoma cells that can be confused with chronic lymphocytic leukemia.[81] • Patients with an unusually indolent form of mantle-cell lymphoma typically present with splenomegaly, bone marrow involvement, and circulating lymphoma cells but without lymphadenopathy and systemic symptoms (so-called non-nodal mantle-cell lymphoma). These mantle-cell lymphomas are rare, and usually have an indolent clinical course and do not require immediate therapy.
Important co-morbidities	• In a population-based study in Sweden, all 1385 patents diagnosed with MCL between 2000 and 214 were identified.[82] In total 44% of the patients had a comorbidity at the time of diagnosis, including a prior malignancy (17%), prior coronary heart disease (14%), concomitant diabetes (9%), history of cerebrovascular disease (6.8%), pulmonary diseases (7%), atrial fibrillation (6.5%), and psychiatric disorders (2.4%).

2.2 Nonclinical Part of the Safety Specification

Full details of the nonclinical safety data for liso-cel are presented in the Nonclinical Overview (Marketing Authorisation Application [MAA], Module 2, Section 2.4 Nonclinical Overview).

A summary of the nonclinical findings and their relevance to human usage is outlined in Table 2.2-1.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
Toxicity Including: Single and Repeat-dose Toxicity • Due to the lack of species cross-reactivity and the underlying nature of this autologous T-cell-based treatment, which prevents persistence of the product in immunocompetent animals, traditional toxicity and pharmacokinetic (PK) studies with liso-cel were deemed inadequate and were expected to provide limited information. Thus, no in vivo nonclinical general safety, genotoxicity, carcinogenicity, developmental safety or reproductive safety studies were conducted. • Due to the autologous nature of liso-cel and its absence of crossreactivity towards CD19 from non human species, single- and repeat-dose toxicity studies were not conducted. Reproductive and Developmental Toxicity • -In the absence of a relevant animal model for assessing the safety of lisocel, no studies have been conducted to assess potential effects of this product on fertility, embryonic development, prenatal and postnatal development, or juvenile	Preclinical models for testing CAR T-cells are currently limited to the xenotransplantation of human CAR T-cells into immunocompromised murine models. It should be noted these experimental systems are limited in their ability to fully model on target/off-tumour toxicity observed in Phase 1 clinical trials, such as Cytokine Release Syndrome (CRS) and neurologic toxicity (NT). Alternative animal models (eg, immune competent rodents, dog, and monkey) are not available at this time. Specifically, nonhuman primate CD19 does not contain the target sequence for liso-cel.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
development. The potential theoretical risks for adverse reproductive and developmental outcomes associated with liso-cel therapy include effects from conditioning and lymphodepleting chemotherapeutic agents such as cyclophosphamide and fludarabine which both have known embryotoxic and teratogenic effects.[83,84] Genotoxicity/Carcinogenicity Genotoxicity: liso-cel is a cellular product and traditional genotoxicity studies (eg, Ames assay, clastogenicity assessments) have not been conducted. Consistent with guidance under "Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products",[85] an exhaustive assessment for genomic insertion sites for liso-cel in transduced patient T-cells has been conducted. • Liso-cel is manufactured using a third-generation, replication incompetent self-inactivating lentiviral vector, which carries minimal risk of horizontal and/or vertical lentivirus transmission, including to persons that handle or administer the gene therapy product, those involved in patient care, relatives, and others. The theoretical risk of insertional oncogenesis associated with the development of replication competent lentivirus (RCL) is minimised by vector engineering and control strategies, which was confirmed for liso-cel by the results of insertion site analysis studies using next-generation sequencing and mapping of lentiviral integration sites. Carcinogenicity: liso-cel has not been evaluated in traditional carcinogenicity studies. Additionally, the absence of cross reactivity of the scFv binder, FMC63, for non-human CD19 and the nature of the therapy as a human cellular product limit the utility of traditional nonclinical models for informing carcinogenicity risk. • An assessment of the carcinogenicity potential of liso-cel was conducted by considering the risk to patients from lymphodepleting chemotherapy (LDC), B-cell aplasia, the pharmacology of the CAR T-cells, and the potential for both lentiviral transduction/insertional oncogenesis and interleukin (IL) -2 independent CAR T-cell proliferation and transformation. The transduction of human T-cells with the liso-cel v20006 lentiviral vector exhibits a genomic integration profile, similar to that reported for wildtype lentiviruses. The absence of evidence of construct-specific risk or enrichment in regions associated with proto-oncogenes, cancer associated common insertion sites or growth-control indicates a low risk of insertional oncogenesis, across a range of vector copy number levels, upon viral transduction of patient T-cells. These data were further supported with an in vitro experiment demonstrating that prolonged culture of liso-cel cells requires IL-2 supplementation, with no evidence of IL-2-independent transformation.	

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
General Safety Pharmacology	
Cardiovascular • Standard safety pharmacology studies with liso-cel were not conducted.	Not applicable
Nervous System • Standard safety pharmacology studies with liso-cel were not conducted.	Not applicable
Other Toxicity-related Information or Data	
Because single- and repeat-dose toxicity studies were not conducted, local tolerance could not be assessed. Nonclinical studies of human autologous CAR T-cells are necessarily limited due to the nature of the agent. For this reason, no carcinogenicity or mutagenicity studies of liso-cel in animals, and no studies on the effects of liso-cel on fertility, have been conducted. Preclinical models for testing CAR T-cells are currently limited to the xenotransplantation of human CAR T-cells into immunocompromised murine models.	CD19 is a 95-kDa glycoprotein present on B-cells from early development until differentiation into plasma cells.[86] It is a member of the immunoglobulin superfamily and a component of a B-cell surface signal transduction complex that positively regulates signal transduction through the B-cell receptor.[86,87] CD19 is an attractive therapeutic target because it is expressed in most B-cell malignancies.[88, 89, 90] Importantly, the CD19 antigen is not expressed on hematopoietic stem cells or on any normal tissue apart from cells of the B-cell lineage.[91]

2.3 Clinical Trial Exposure

2.3.1 Clinical Study Information

An overview of the liso-cel clinical program summarized in this RMP is in Table 2.3.1-1.

Table 2.3.1-1: Liso-cel Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number	Study Title/Design	Number Treated Subjects[a]
2L LBCL		
Study JCAR017-BCM-003 (TRANSFORM; hereafter referred to as Study BCM-003)[b]	A Phase 3, randomized, multicenter trial to compare the efficacy and safety of liso-cel to standard of care in subjects with high risk, transplant eligible R/R aggressive B-cell NHL.	Liso-cel: 89 (Arm B)
Study 017006 (TRANSCEND-PILOT-017006)	A Phase 2 Study of lisocabtagene maraleucel of lisocabtagene maraleucel (JCAR017) as second-line therapy in adult patients with aggressive B-cell NHL	Liso-cel: 61

Table 2.3.1-1: Liso-cel Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number	Study Title/Design	Number Treated Subjects[a]
Study JCAR017-BCM-001 (TRANSCEND WORLD; hereafter referred to as Study BCM-001)	A Phase 2, open-label, single arm study of liso-cel monotherapy. Similar to Study 017001, cohorts 1 (Europe) and 3 (Japan) are in subjects with R/R B-cell lymphoma after 2 or more systemic lines of therapy.	Liso-cel: 27 (Cohort 2)
3L+ DLBCL		
Study 017001 (TRANSCEND)	A Phase 1, open-label, single-arm study of liso-cel monotherapy in subjects with R/R B-cell lymphoma after 2 or more systemic lines of therapy	Liso-cel: 270 (DLBCL Cohort)
Study BCM-001	A Phase 2, open-label, single arm study of liso-cel monotherapy. Similar to Study 017001, cohorts 1 (Europe) and 3 (Japan) are in subjects with R/R B-cell lymphoma after 2 or more systemic lines of therapy. Cohort 1 provides clinical experience with the manufacturing process in the EU where a contract manufacturing organisation (Cellex) is used for the front end processing.	Liso-cel: 55 (Cohorts 1, 3, and 7)
Study JCAR017-BCM-002 (PLATFORM; hereafter referred to as Study BCM-002)	An exploratory Phase 1/2 trial to evaluate the safety and efficacy of liso-cel combinations in subjects with R/R B-cell malignancies	Liso-cel: 26
Study 017007 (TRANSCEND-OUTREACH)	A Phase 2 open-label, single-arm study, to determine the safety and efficacy of liso-cel in adult subjects with R/R large B-cell lymphoma (LBCL) after 2 systemic lines of therapy in the outpatient setting	Liso-cel: 80
2L+ FL		
Study JCAR017-FOL-001 (TRANSCEND FL; hereafter referred to as Study FOL-001)	A Phase 2, open-label, multi-cohort, multicenter study to evaluate the efficacy and safety of liso-cel in adult subjects with R/R FL or marginal zone lymphoma (MZL).	Liso-cel: 130 (FL cohorts; Cohorts 1, 2, and 3)
3L+ MCL		
Study 017001 (TRANSCEND-MCL Cohort)	A Phase 1, Multicenter, Open-Label Study of JCAR017, CD19-targeted Chimeric Antigen Receptor (CAR) T Cells, for Relapsed and Refractory (R/R) B-cell Non-Hodgkin Lymphoma (NHL)	Liso-cel: 88 (MCL Cohort)

[a] Data cutoff: 13-May-2022 for BCM-003 and LTFU BCM-003, 02-Mar-2022 for BCM-001 and LTFU BCM-001, 24-Sep-2021 for 017006, 017007, and for LTFU 017006 and LTFU 017007, 04-Jan-2021 for 017001 (LBCL Cohort) and LTFU 017001 (LBCL Cohort), 01-Aug-2019 for BCM-002, 10-Jan-2024 for FOL-001 and 31-Jan-2023 for LTFU FOL-001 (LTFU = GC-LTFU-001), 16-May-2024 for 017001 (MCL Cohort) and 31-Jan-2024 for LTFU 017001 (MCL Cohort)

[b] In Study BCM-003, safety data are presented for 183 subjects from time of randomization (92 and 91 subjects in the liso-cel and SOC arms, respectively). Of the 92 randomized subjects in the liso-cel arm, 89 subjects received liso-cel infusion.

2.3.2 Clinical Trial Exposure

The overall safety analysis presents data for 826 subjects exposed to liso-cel across the 7 clinical trials as presented in Table 2.3.1-1. Three dose levels were evaluated across the 7 clinical studies in: Dose Level 1 (DL1), 50 × 10^6 CAR+ T-cells, Dose Level 2 (DL2), 100 × 10^6 CAR+ T-cells, and Dose Level 3 (DL3), 150 × 10^6 CAR+ T-cells. Study 017001 evaluated all three dose levels, BCM-002 evaluated DL1 and DL2, and BCM-001, 017007, Study 017006, BCM-003, and FOL-001 evaluated DL2 only.

The tabulated list of adverse reactions in the Summary of Product Characteristics (SmPC; Table 3) based on pooled data from 7 studies (017001, BCM-001, BCM-002, 017007,017006, BCM-003, and FOL-001) was updated to reflect data from 738 patients within the dose range of 44 to 120 × 10^6 CAR+ viable T-cells (DL1 and DL2).

Liso-cel exposure is defined as the duration of follow-up post initial administration of liso-cel with proliferation *in vivo* thereafter and persistence in peripheral blood and/or extravascular tissues thereafter.

Exposure is presented by duration in Table 2.3.2-1, dose in Table 2.3.2-2, age group and gender in Table 2.3.2-3 and race and ethnic origin in Table 2.3.2-4

Table 2.3.2-1: Duration of Exposure (Pooled 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Treated Set)

Duration of Exposure	Persons (N = 826)	Percentage
Subjects received at least 1 cycle[a]	826	100
Subjects received retreatment cycles[b]	21	2.5

[a] 1 cycle = liso-cel infusion

[b] In Study 017001 and 017006, retreatment with liso-cel was allowed for subjects who achieved complete response after liso-cel treatment and subsequently had progressive disease.

Table 2.3.2-2: Exposure Administered Dose (Pooled 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Treated Set)

Parameter	Persons	Mean Volume in ml (SD)	Cell dose (×10^6 CAR+ T-cells; Median, Range)
Cycle 1 Dose 1			
CD8	826	2.76 (1.967)	49.5 (16, 134)
CD4	826	2.01 (1.067)	49.5 (20, 107)
Total	**826**	**4.76 (2.641)**	**99.3 (37, 241)**

Table 2.3.2-3: Duration of Follow-up by Age Group and Gender (Pooled 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Treated Set)

Age Group	Persons		Person Time (PY of Follow-up)[a]	
	Male	Female	Male	Female
< 65 years	259	147	378.5	216.1
>= 65 to < 70 years	93	55	115.0	97.7
>= 70 to < 75 years	105	51	143.7	57.0
>= 75 to < 85 years	70	43	79.6	53.6
>= 85 years	0	3	0.0	1.8
Total	**527**	**299**	**716.8**	**426.2**

[a] PY which is calculated as sum of study follow-up time across treated subjects. The follow-up time is (EOS date - first JCAR017 dose date + 1)/365.25 for subjects who did not enroll in the LTFU. If a subject is ongoing in the study, the earliest of (the last known alive date, data cutoff date) is used to impute the EOS date for the purpose of the calculation. For subjects who enrolled in the LTFU study, the follow-up time is (min (last known alive date, death date, data cutoff date) - first dose date + 1)/365.25).

Table 2.3.2-4: Duration of Follow-up by Race and Ethnicity (3L+ MCL, 2L+ FL and 2L/3L+ LBCL Treated Set)

	Persons	Person Time (PY of Follow-up)[a]
Race		
White	631	851.8
Asian	55	80.3
Black or African American	28	40.7
American Indian or Alaska Native	2	2.3
Native Hawaiian or Other Pacific Islander	1	2.0
Multiple	1	2.0
Other	3	3.6
Not provided[b]	105	160.3
Total	**826**	**1143.0**
Ethnicity		
Hispanic or Latino	64	76.2
Not Hispanic or Latino	664	906.0
Not provided [b]	98	160.8
Total	**826**	**1143.0**

[a] PY which is calculated as sum of study follow-up time across treated subjects. The follow-up time is (EOS date - first JCAR017 dose date + 1)/365.25 for subjects who did not enroll in the LTFU. If a subject is ongoing in the study, the earliest of (the last

known alive date, data cutoff date) is used to impute the EOS date for the purpose of the calculation. For subjects who enrolled in the LTFU study, the follow-up time is (min (last known alive date, death date, data cutoff date) - first dose date + 1)/365.25).

[b] 'Not Collected' and 'Unknown' were combined into the 'Not provided' category.

PY = patient years

2.4 Populations Not Studied in Clinical Trials

2.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Pregnant and lactating women	Pregnant and lactating females are excluded to avoid potential harm to the unborn foetus or breastfeeding newborn.	Yes	N/A
Inadequate hepatic function defined by alanine aminotransferase (ALT) greater than or equal to 5 × upper limit of normal (ULN) and total bilirubin greater than 2.0 mg/dL (or greater than 3.0 mg/dL for subjects with Gilbert's syndrome or lymphomatous infiltration of the liver)	Cytokine release syndrome can be associated with hepatotoxicity which may predispose to adverse events (AEs) in subjects with pre-existing hepatic impairment.	No	Hepatic metabolism is not known to be a major clearance pathway for CAR T-cells and has not been studied.
Hypersensitivity to the active substance or to any of the excipients	Increases the risk for a clinically important hypersensitivity reaction.	No	Liso-cel is contraindicated in patients with hypersensitivity to any of the product excipients (SmPC Section 4.3).
Acute HIV, hepatitis B virus (HBV) or HCV infection at the time of screening	Immunosuppression after liso-cel infusion could lead to exacerbation of active HIV, HBV or HCV infections.	No	Patients with HIV and HCV infection will not be treated with liso-cel, as the leukapheresis material from patients with a positive HIV or HCV test will not be accepted for manufacturing. Therefore, treatment in this non-target population is not considered missing information, as these patients will not be exposed and experience potential exacerbation of the pre-existing viral infection. Screening for HIV, active HBV and active HCV must be performed before collection of cells for manufacturing. Leukapheresis material from patients with active HIV or active HCV infection will not be

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
			accepted for manufacturing (SmPC Sections 4.2 and 4.4). With regard to patients with active HBV, as the product should not be administered to patients with active infections this population was excluded from the clinical trial setting as HBV reactivation, in some cases may result in fulminant hepatitis, hepatic failure or death, which can occur in patients treated with medicinal products directed against plasma cells/B cells. Patients with pre-existing HBV infection without active disease (as defined by absence of significantly elevated transaminase enzymes and undetectable HBV DNA) were eligible for inclusion in the clinical trial setting. These patients should be monitored for signs and symptoms of infection before and after infusion and treated appropriately. Prophylactic, pre-emptive and/or therapeutic antivirals should be administered according to institutional guidelines in line with guidelines from the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver and the American Society of Clinical Oncology. In the Pooled 2L and 3L+ LBCL Treated Set, none of the 17 identified HBV infected subjects had AEs reported after liso-cel therapy that were considered consistent with Hepatitis B reactivation. Two subjects in the 017001 liso-cel-treated set had a history of Hepatitis C and none had findings suggesting worsening of hepatitis after liso-cel treatment. Warnings regarding infection and viral reactivation have been included in Section 4.4 of the SmPC.

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Uncontrolled systemic fungal, bacterial, viral or other infection despite appropriate antibiotics and/or other treatment at the time of leukapheresis or liso-cel administration	A reduction in peripheral blood B lymphocytes and immunoglobulins is an expected on target pharmacodynamic effect of liso-cel therapy. In addition, the conditioning LDC with fludarabine and cyclophosphamide promotes cytopenia that can also increase the risk of infection. Immunosuppression after liso-cel could lead to exacerbation of, or diminished capacity for, clearance of uncontrolled infections.	No	Warnings regarding infection and viral reactivation have been included in Section 4.4 of the SmPC.
Severe renal insufficiency	In Studies 017001, BCM-001, 017006, and 017007, subjects with severe renal insufficiency, calculated creatinine clearance (Cockcroft and Gault method) < 30 mL/min/1.73 m^2 were excluded because of the potential for fludarabine toxicity despite dosing adjustment, and because lower doses of fludarabine may provide suboptimal conditioning and impact liso-cel treatment outcomes. In Study BCM-002, subjects with calculated creatinine clearance (Cockcroft and Gault method) < 60 mL/min were excluded. In Study BCM-003 eligibility criteria required subjects to have serum creatinine < 1.5 x ULN or creatinine clearance > 45 mL/min.	No	Reference to fludarabine dose adjustment in renal impairment is included in Section 4.2 of the SmPC.
Presence of acute or chronic graft-versus-host disease (GvHD)	It is not known if liso-cel cells manufactured from allogenic donor T-cells (ie transplanted bone marrow) could potentially cause or worsen GvHD.	No	Liso-cel has not been studied in patients who have undergone allo-HSCT within 90 days of leukapheresis, or who have received a donor lymphocyte infusion with 6 weeks of liso-cel administration or in patients with active GvHD.

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
			SmPC Section 4.4 states that infusion is not recommended in patients with active acute or chronic GvHD.
Allogenic HSCT within 90 days of leukapheresis. Donor lymphocyte infusions within 6 weeks of liso-cel administration	Clinical stability and recovery from allo-HSCT toxicities were required at the time of liso-cel infusion, and sufficient time had to elapse following HSCT to be able to exclude subjects with acute GvHD.	No	Liso-cel has not been studied in patients who have undergone allo-HSCT within 90 days of leukapheresis, or who have received a donor lymphocyte infusion within 6 weeks of liso-cel administration or in patients with active GvHD. SmPC Section 4.4 states that infusion is not recommended in patients with active acute or chronic GvHD.
History of any one of the following cardiovascular conditions within the past 6 months: Class III or IV heart failure as defined by the New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease	Clinically stability and adequate cardiac reserve required at the time of liso-cel infusion.	No	Section 4.4 of the SmPC states that liso-cel infusion should be delayed in cases of unresolved serious adverse events, including cardiac events.
History or presence of clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis	Although patients with secondary CNS involvement were included in the clinical studies, it is unknown whether liso-cel treatment of patients with other pre-existing CNS conditions would heighten the risk of such conditions worsening or if such conditions might predispose to the development of CAR T-cell associated NT.	No	Section 4.4 of the SmPC contains advice regarding NT.

2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse drug reactions (ADRs) such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

2.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

To ensure patient safety, specific populations of patients were excluded from the pivotal and supportive studies (Table 2.4.3-1). Thus, experience in these populations is limited.

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	Not included in the clinical development programme.
Patients with relevant comorbidities	
Patients with renal impairment	Studies 017001, BCM-001, 017007, BCM-002, 017006 and BCM-003 had entry criteria for renal function, measured by either serum creatinine or calculated creatinine clearance. In Studies 017001, BCM-001, 017006 and 017007, subjects were required to have serum creatinine < 1.5 × age-adjusted ULN or calculated creatinine clearance (Cockcroft and Gault) > 30 mL/min/1.73 m^2. Study BCM-002 eligibility criteria required subjects to have creatinine clearance ≥ 60 mL/min. Study BCM-003 eligibility criteria required subjects to have serum creatinine < 1.5 x ULN or creatinine clearance > 45 mL/min.
Patients with severe renal impairment	Not included in the clinical development programme. See renal impairment section above.
Patients with hepatic impairment	Studies 017001, BCM-001, 017007, BCM-002, 017006 and BCM-003 had entry criteria for hepatic function, as defined by upper acceptable limits of liver function tests, serum ALT, and total serum bilirubin. In all studies subjects were required to have ALT ≤ 5 × ULN and total bilirubin < 2.0 mg/dL (or < 3.0 mg/dL for subjects with either Gilbert's syndrome or lymphomatous infiltration of the liver).
Patients with severe hepatic impairment	Not included in the clinical development programme.
Patients with cardiovascular impairment	Studies 017001, BCM-001, 017007, 017006, and BCM-002 required subjects to have adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥ 40% as assessed by echocardiogram of multiple update gated acquisition (MUGA) scan performed within

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	1 month of determination of eligibility (1 month prior to apheresis). BCM-003 required subjects to have this assessment performed within 4 weeks of randomization. Subjects with history of Class III or IV heart failure as defined by the NYHA or subjects with active ischaemic heart disease as defined by cardiac angioplasty, stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease within the past 6 months were excluded from the studies.
Immunocompromised patients	The target population used in the clinical trial development programme was immunocompromised patients because of underlying lymphoma and prior immunosuppressive therapies, often with cytopenia and hypogammaglobulinaemia present at the time of apheresis and lymphodepletion and/or liso-cel infusion.
Patients with a disease severity different from inclusion criteria in clinical trials	The studies did not exclude subjects based on disease stage or severity. Of all the subjects included in the 2L and 3L+ LBCL clinical studies, subjects generally had advanced stage disease. Subjects with secondary CNS lymphoma involvement were not excluded from these studies. Subjects with ECOG performance scores of 3 or 5 were excluded.
Population with relevant different ethnic origin	Included in clinical development programme. See Table 2.3.2-4.
Subpopulations carrying relevant genetic polymorphisms	Liso-cel is not known to be metabolised by hepatic cytochrome P450 enzymes. The effect of genetic polymorphisms has not been studied in the liso-cel clinical trials.
Other	**Paediatric Population:** Liso-cel is not authorised for use in children in the EU/EEA or elsewhere in the world but is being evaluated in paediatric patients with B-cell malignancies. There is limited experience with liso-cel from one company-sponsored trial in children. As of May-2023, 13 paediatric subjects were treated in Study JCAR017-BCM-004. The study was terminated as the EMA has waived the obligation of a paediatric investigation plan for liso-cel in all paediatric populations based on the grounds that no significant benefit can be expected over existing therapies.

2.5 Post-Authorisation Experience

Liso-cel is authorised in the US (05-Feb-2021), Japan (22-Mar-2021), Switzerland (28-Mar-2022), the EU (04-Apr-2022), Canada (06-May 2022), and Great Britain (26-Oct-2023). In the postauthorisation phase, active pharmacovigilance and surveillance of literature and spontaneous

reports as well as reports from the additional pharmacovigilance activities, will be used to monitor for potential off-label use outside of clinical studies. Evaluation of on-label and off-label liso-cel use, including use in special populations mentioned in the RMP, and associated safety observations, will be represented in the Periodic Safety Update Report (PSUR).

2.5.1 Post-authorisation Exposure

2.5.1.1 Method Used to Calculate Exposure

The estimate of patient exposures from commercial experience is based on controlled manufacturing and shipment reporting provided to the MAH. The estimate was obtained by querying the resulting database for shipments of commercial liso-cel to treatment sites with dates on or before 04-Aug-2024.

2.5.1.2 Exposure

Overall, estimated cumulative commercial exposure to liso-cel as of 04-Aug-2024 is approximately 2,556 patients Table 2.5.1.2-1. The cumulative value for exposure represents the estimated number of unique patients exposed to the product from IBD 05-Feb-2021 through 04-Aug-2024.

Table 2.5.1.2-1: Summary of Worldwide Estimate Number of Patients Commercially Exposed

Region	Cumulative Exposure (05-Feb-2021 to 04-Aug-2024)[a]	
	Conforming	Nonconforming
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[a] The cumulative numbers are an estimation and are not meant to be additive between consecutive reports due to delays in information transfer from treatment sites to the MAH.

[redacted] amed-patient programs and is not counted under commercial exposure.

[redacted].

2.6 Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

Liso-cel has not been systematically studied in humans for its potential for abuse, tolerance or physical dependence. Based on its pharmacological properties, there is no anticipated risk of abuse or misuse for illegal purposes. Liso-cel is an intra-patient autologous product manufactured from individual patient T-cells and distributed via a controlled access programme.

2.6.2 Flow-chart of the Logistics of the Therapy

Figure 2.6.2-1: Arm-to-arm Liso-cel Process

2.6.3 Risks to Living Donors

After the leukapheresis procedure, the patient may experience temporary discomfort, including irritating, swelling or bruising at the place where the needle was inserted into the vein to collect the blood. Leukapheresis can also occasionally cause nausea, vomiting, fainting, seizures, blood loss, infection, skin rash, flushing, hives, numbness and tingling, or swelling of the feet or ankles. These symptoms are generally mild and go away during the procedure or shortly thereafter.

2.6.4 Risks to Patients in Relation to Quality Characteristics, Storage and Distribution of the Product

Liso-cel is manufactured using a third-generation, replication incompetent self-inactivating lentiviral vector, which carries minimal risk of horizontal and/or vertical lentivirus transmission, including to persons that handle or administer the gene therapy product, those involved in patient care, relatives, and others.

- The risks to patients related to quality characteristics, storage, distribution, and administration procedures are addressed in Table 2.7.3.1-15 (Reduced Viability of Liso-cel due to Inappropriate Product Handling). Liso-cel cells can lose viability due to inappropriate

temperature during transport and storage, including due to inadequate thawing, preparation, and infusion of the product.

- Routine risk minimisation measures that address these potential risks include the following sections of the SmPC and package leaflet (PL):
  - Section 4.2 (SmPC) Posology and method of administration for information on preparation and administration.
  - Section 6.3 (SmPC) Shelf-life for information on shelf-life of unopened and thawed liso-cel. The product should be administered immediately after thawing.
  - Section 6.4 (SmPC) Special precautions for storage for information on storage and transport of liso-cel in the vapour phase of liquid nitrogen.
- Section 6.5 (SmPC) Nature and contents of container for information on how liso-cel is supplied.
- Section 6.6 (SmPC) Special precautions for disposal and other handling for information on the preparation, thawing and handling of liso-cel.
  - Section 5 (PL) How to store liso-cel for information on storage of liso-cel in the vapour phase of liquid nitrogen.
  - In the section for healthcare professionals (HCPs) only within the PL, information is provided on handling, accidental exposure and disposal of liso-cel.

2.6.5 Risks to Patients Related to Administration Procedures

The risks to patients related to administration procedures can be categorized as risks related to conditioning of the patient and risks related to mistakes or violations of the standard procedures for administration of the product (eg, different administration procedures used by different healthcare establishments/HCPs resulting in differing results).

- Risks related to conditioning of the patient include risks associated with the LDC:
  - In Study 017001, 75.5% of subjects experienced an AE related to LDC. The 3 most frequently reported AEs were nausea (38.3%), anaemia (30.9%), and fatigue (29.2%). In Study BCM-001, 66.7% of subjects in Cohorts 1 and 3 experienced an AE related to LDC (data cut off 04-Jan-2021 for both studies).
  - In the Interim Analysis of Study BCM-003, 83.7% of subjects in the liso-cel arm experienced an AE related to cyclophosphamide. The 3 most frequently reported AEs were neutropenia (59.8%), anaemia (39.1%) and nausea (35.9%). 84.8% of subjects in the liso-cel arm experienced an AE related to fludarabine. The 3 most frequently reported AEs were neutropenia (63.0%), anaemia (40.2%) and nausea (35.9%).
  - In the Primary Analysis of Study BCM-003, the overall frequency of AEs related to LDC reported in the liso-cel arm was consistent with the Interim Analysis.
  - In Study FOL-001. 75.4% of all subjects experienced an AE related to LDC. The 3 most frequently reported AEs were neutropenia (53.1%), anaemia (29.2%), and thrombocytopenia (15.4%).
  - In Study 017006, in the period from leukapheresis to the day prior to LDC, 10 (13.5%) subjects experienced at least 1 AE. The most frequently occurring AEs by SOC were general disorders and administration site conditions (6 [8.1%] subjects) and metabolism,

nutrition disorders (4 [5.4%] subjects). During this time period, 3 (4.1%) subjects had LDC-related AEs (these subjects underwent LDC twice). Four (5.4%) subjects had SAEs, including 1 (1.4%) subject who had an LDC-related SAE. One (1.4%) subject had a Grade 5 AE of pneumonia that was not considered to be LDC-related. In the period from the start of LDC to the day prior to liso-cel infusion, 57 (90.5%) subjects had at least 1 AE and the most frequently occurring AEs by SOC were gastrointestinal disorders (36 [57.1%] subjects), blood and lymphatic system disorders (20 [31.7%] subjects), and general disorders and administration site conditions (19 [30.2%] subjects). During this time period, 43 (68.3%) subjects had LDC-related AEs. Four (6.3%) subjects had SAEs, including 2 (3.2%) subjects who had LDC-related SAEs.

- In study BCM-001 Cohort 2, 18.5% of the subjects of the liso-cel treated subjects experienced an AE between leukapheresis until the day before the start of LDC. In addition, 88.5 % of the subjects of the liso-cel treated subjects (from first day of LDC until the day prior to liso-cel infusion) experienced an AE. The 3 most frequently reported AEs were nausea (30.8%), anaemia (26.9%), and fatigue, lymphopenia and neutropenia (11.5% each).
- In study FOL-001, 13.0% of 2L+ subjects treated with liso-cel experienced an AE between leukapheresis until the day before the start of LDC and none were Grade <=3. In addition, 87.0% of 2L+ subjects treated with liso-cel experienced an AE between the first day of LDC until the day prior to liso-cel infusion; 17.4% of these were Grade 3-4.
- In study 017001 MCL cohort, in the period from lymphodepletion to liso-cel infusion, 61.3% subjects experienced any LDC-related related AE. 23.7% of subjects experienced a Grade 3 or 4 AEs related to LDC with no Grade 5 LDC-related AEs.

- Routine risk communication related to the LDC is provided in the SmPC in the following sections:
  - Section 4.2 Posology and method of administration for information on the LDC regimen.
  - Section 4.3 Contraindications advising that contraindications to LDC must also be considered.
  - Section 4.4 Special warnings and precautions for use for information on prolonged cytopenia.
  - Section 4.5 Interaction with other medical products and other forms of interaction for information on vaccination with live virus.
  - Section 4.6 Fertility, pregnancy and lactation for information regarding the use of effective contraception.

Risks related to mistakes or violations of the standard procedures for administration of the product include the risk of medication errors.

- The liso-cel supply chain is designed and managed to ensure chain of identity and custody from apheresis, to T-cell isolation, to manufacturing and then back to the clinical centre for administration. To ensure traceability, the name of the product, the batch number and the name of the treated patient should be kept for a period of 30 years.
- Liso-cel is composed of CAR+ viable T-cells formulated as separate CD8+ and CD4+ cell components; there is a separate Release for Infusion Certificate (RfIC) for each cell component. The RfIC provides information on the number of syringes needed and the volume

to be administered of the CD8+ and CD4+ cell components. Before thawing the vials, the patient's identity is confirmed with the patient identifiers on the shipper, external carton and RfIC.

- Administration of liso-cel may cause infusion related reactions, including fever, rigors, rash, urticaria, dyspnoea, hypotension, and/or nausea. Patients are to be premedicated with paracetamol and diphenhydramine or another H1-antihistamine before the infusion.

In addition, routine risk communication related to infusion reactions is provided in the SmPC and PL in the following sections:

- Section 4.2 (SmPC) Posology and method of administration for pre-medication with paracetamol and diphenhydramine or another H1-antihistamine before infusion of liso-cel.
- Section 4.8 (SmPC) Undesirable effects for information on infusion related reactions.
- Section 3 (PL) How liso-cel is given for information on pre-medication with paracetamol and an antihistamine medicine before infusion to reduce risk of infusion reactions.
- Section 4 (PL) Possible side effects for information on common side effects including infusion reactions.

2.6.6 Risks Related to Interaction of the Product and the Patient

- The risks to patients related to interaction of the product and the patient are addressed in Section 2.7.3.1 through the important identified risks of CRS (Table 2.7.3.1-1), NT including ICANS (Table 2.7.3.1-2), infections (Table 2.7.3.1-3), hypogammaglobulinemia (Table 2.7.3.1-4), macrophage activation syndrome (MAS) (Table 2.7.3.1-5), tumour lysis syndrome (TLS) (Table 2.7.3.1-6), cytopenia (Table 2.7.3.1-7), secondary malignancy of T-cell origin (Table 2.7.3.1-8) and the important potential risks of autoimmune disorders (Table 2.7.3.1-9), aggravation of GvHD (Table 2.7.3.1-10), secondary malignancy (except secondary malignancy of T-cell origin) (Table 2.7.3.1-11), generation of replication competent lentivirus (Table 2.7.3.1-12), immunogenicity (Table 2.7.3.1-13), transmission of infectious agents (Table 2.7.3.1-14), and reduced viability of liso-cel due to inappropriate product handling (Table 2.7.3.1-15).
- Routine risk communication that addresses the risks through the SmPC are in the following sections:
  - Section 4.2 Posology and method of administration for the risks of CRS, NT including ICANS and other toxicities.
  - Section 4.4 Special warnings and precautions for use for the risks of CRS, NT including ICANS, infections, cytopenias, secondary malignancy of T-cell origin, hypogammaglobulinemia, hypogammaglobulinemia, MAS, secondary malignancies (except secondary malignancy of T-cell origin), TLS, and aggravation of GvHD.
  - Section 4.8 Undesirable effects for information on CRS, NT including ICANS, infections, hypogammaglobulinemia, MAS, TLS, cytopenia and the important potential risk of autoimmune disorders.
- Additional risk minimisation measures are implemented through a Controlled Distribution Programme, HCP Education Programme, and Patient Educational Programme addressing the risk of CRS and NT including ICANS.

- The risks of autoimmune disorders and generation of replication competent lentivirus are addressed by conducting active monitoring with routine pharmacovigilance and additional pharmacovigilance activity (Study GC-LTFU-001).

2.6.7 Risks Related to Scaffolds, Matrices and Biomaterials

- The risk to patients related to biomaterials is addressed through the important identified risk of secondary malignancy of T-cell origin (Table 2.7.3.1-8) and the important potential risks of secondary malignancies (except secondary malignancy of T-cell origin) (Table 2.7.3.1-11) and transmission of infectious agents (Table 2.7.3.1-14).
- Routine risk minimisation measures that address this potential risk include the following section of the SmPC:
  - Section 4.2 Posology and method of administration.
  - Section 4.4 Special warnings and precautions for use.

2.6.8 Risks Related to Persistence of the Product in the Patient

- The risks to patients related to the persistence of the product in the patient are addressed through the important identified and potential risks of infections (Table 2.7.3.1-3), cytopenia (Table 2.7.3.1-7), secondary malignancy of T-cell origin (Table 2.7.3.1-8), autoimmune disorders (Table 2.7.3.1-9), secondary malignancy (except secondary malignancy of T-cell origin) (Table 2.7.3.1-11), and generation of replication competent lentivirus (Table 2.7.3.1-12).
- Routine risk communication that addresses the risk through the SmPC are in the following sections:
  - Section 4.4 Special warnings and precautions for use for the risk of secondary malignancy of T-cell origin and secondary malignancy (except secondary malignancy of T-cell origin).
  - Section 4.8 Undesirable effects for the risks of infections and cytopenia.
- The risks of autoimmune disorders and generation of replication competent lentivirus are addressed by conducting active monitoring with routine pharmacovigilance and additional pharmacovigilance activity (Study GC-LTFU-001).

2.6.9 Risks to Healthcare Professionals, Care Givers, Offspring and Other Close Contacts with the Product or Its Components, or with Patients

- The risks to HCPs, care givers, and other close contacts with the product or its components, or with patients is addressed through the important potential risk of transmission of infectious agents (Table 2.7.3.1-14).
- Groups exposed to this identified potential risk include individuals in close contact with liso-cel including HCPs involved in the thawing, preparation and administration of the product.
- Routine risk communication that addresses this risk through the SmPC and PL are in the following sections:
  - Section 4.2 (SmPC) Posology and method of administration which indicates that liso-cel must be administered at a qualified treatment centre and treatment initiated under the direction and supervision of a HCP experienced in the treatment of haematological malignancies and trained for administration and management of liso-cel.

- Section 4.4 (SmPC) Special warnings and precautions for use which includes guidance proscribing blood, organ, tissue and cell donation and the requirement to screen for HBV, HCV and HIV prior to cell collection for manufacturing.
- Section 6.6 (SmPC) Special precautions for disposal and other handling which describes liso-cel as genetically modified human blood cells and outlines the requirement to follow local guidelines for disposal of unused medicinal product and all material that has been in contact with it and decontamination of surfaces with disinfectant. Precautionary measures to be taken when handling the product including wearing gloves, protective clothing, and eye protection to avoid potential transmission of infectious diseases. Information is also provided regarding accidental exposure.
- Section 5 (PL) How to store liso-cel which describes keeping out of the sight and reach of children. Information is also provided regarding disposal of unused medicine or waste material.
- In the section for HCPs only within the PL, information is provided on handling, accidental exposure and disposal of liso-cel.

Only hospitals and their associated centres which have the applicable Genetically Modified Organisms license in accordance with national legislation will be supplied with liso-cel to ensure the appropriate control measures are in place so that the unused medicine and waste material is disposed of in compliance with local guidelines on handling of waste of human-derived material.

2.7 Identified and Potential Risks

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

Safety concerns identified in the initial submission of the RMP are summarized in Table 2.7.1-1.

Table 2.7.1-1: Safety Concerns in the Initial RMP

Important identified risks	Cytokine release syndrome
	Neurologic toxicity
	Infections
	Hypogammaglobulinaemia
	Macrophage activation syndrome/haemophagocytic lymphohistiocytosis
	Tumour lysis syndrome
	Cytopenia, including bone marrow failure
Important potential risks	Autoimmune disorders
	Aggravation of graft versus host disease
	Secondary malignancies/insertional oncogenesis
	Cerebral oedema
	Generation of replication competent lentivirus
	Immunogenicity
	Transmission of infectious agents

Table 2.7.1-1: Safety Concerns in the Initial RMP

	Reduced viability of liso-cel due to inappropriate product handling
Missing information	Impact on pregnancy and lactation
	Long-term safety
	Safety in patients < 18 years old
	Safety in patients ≥ 75 years

2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 2.7.1.1-1: Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Risk	Justification
Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised)	
Hypersensitivity Reactions - Allergic reactions may occur with the infusion of liso-cel. These reactions may be due to dimethyl sulfoxide (DMSO) or the materials used in the liso-cel manufacturing process.	No hypersensitivity reactions due to DMSO or other materials have been reported during liso-cel clinical trials. The SmPC requires that patients be pre-medicated with paracetamol and diphenhydramine or other H1 antihistamine 30 or 60 minutes prior to liso-cel infusion. Prescribers must have appropriate fluids for intravenous (IV) administration and medications available to treat possible allergic reactions or hypersensitivity as part of standard clinical practice supporting infusion.
Hepatitis B or C Reactivation - Depletion of B-cells which is an expected on-target toxicity increases the risk for viral reactivation among patients with prior viral infections such as Hepatitis B or C.	Subjects with inactive hepatitis prior to liso-cel infusion were retrospectively identified in order to determine if any subject had reactivation of latent or suppressed Hepatitis B or Hepatitis C. Ten of 12 identified HBV infected subjects were on one or more suppressive antiviral medications at the time of study enrolment and thereafter, and one was never treated with a hepatitis B antiviral medication after liso-cel treatment. None of the 12 subjects had AEs reported after liso-cel therapy that were considered consistent with hepatitis B reactivation. Similarly, 2 subjects with Hepatitis C prior to liso-cel infusion were retrospectively identified and none had post liso-cel AEs suggesting Hepatitis C exacerbation. The SmPC (Sections 4.2 and 4.4) includes precautionary language for screening of HBV and other viral infections (HCV, HIV) in accordance with clinical guidelines prior to the collection of cells for liso-cel manufacture. Patients with HIV and HCV infection will not be treated with liso-cel as the leukapheresis material from patients with a positive HIV or HCV test will not be accepted for manufacturing (Table 2.4.1-1).

2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Important identified risks	
Cytokine release syndrome	Cytokine release syndrome is an AE associated with CAR T-cell therapies and is a very common AE in subjects treated with liso-cel. In the Pooled 3L+ DLBCL Treated Set, CRS occurred in 41.2% of subjects and the majority of the CRS events were mild to

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
	moderate in severity, with ≥ Grade 3 events in 2.2% of subjects. Potential CRS warrants careful surveillance and prompt management to reduce the possibility of adverse outcomes. Risk management activities (site qualification, HCP education regarding recognition and management of CRS, and patient education) will be implemented and included in approved product labelling. The collection and analysis of safety data from registries and spontaneous reporting will provide additional information to characterise the product safety profile in the commercial setting.
Neurologic toxicity	Neurologic toxicity is an AE associated with CAR T-cell therapies. CAR T-cell-associated NTs, as identified by investigators (investigator identified neurologic toxicity; iiNT), occurred in 27.6% of subjects receiving liso-cel, including ≥ Grade 3 in 9.7% of subjects. Risk management activities (site qualification, HCP education regarding recognition and management of NT, and patient education) will be implemented and included in approved product labelling. The collection and analysis of safety data from registries and spontaneous reporting will further characterise the product safety profile in the commercial setting.
Infections	Infections ≥ Grade 3 occurred in 13.1% of subjects in the Pooled 3L+ DLBCL Treated Set. Liso-cel treated subjects are routinely predisposed to infection because of pre-treatment cytopenia and hypogammaglobulinaemia from prior LDC and lymphoma therapy. In liso-cel clinical trials, subjects were treated with prophylactic antibacterial, antiviral and antifungal agents in accord with local practice guidelines. Infection risk management activities as presently utilised in clinics, hospitals and centres engaged in the treatment of immunocompromised patients with haematologic malignancies are actively reinforced for patients receiving liso-cel treatment.
Hypogammaglobulinaemia	Hypogammaglobulinaemia is anticipated as a liso-cel on target pharmacodynamic effect that is associated with increased risk of infections. In the Pooled 3L+ DLBCL Treated Set, hypogammaglobulinaemia was reported in 12.0% of subjects in the treatment-emergent period, all of which were assessed as mild or moderate in severity (ie, < Grade 3). Liso-cel prescribers should monitor for infections and patient immunoglobulin levels and utilise immunoglobulin replacement therapy in accordance with local guidelines.
Macrophage activation syndrome/haemophagocytic lymphohistiocytosis	Macrophage activation syndrome/haemophagocytic lymphohistiocytosis is a potentially life-threatening inflammatory syndrome marked by proliferation and activation of lymphocytes and macrophages and was uncommonly observed in the Pooled 3L+ DLBCL Treated Set (2 cases reported from 359 subjects, both from Study BCM-001 and both confounded by Grade 4 or 5 fungal infection and progressive disease). Successful management of MAS/HLH by liso-cel prescribers will include prompt treatment of worsening CRS, early recognition of MAS/HLH, treatment of MAS/HLH triggers such as infection, and escalating therapy per guidelines as required.
Tumour lysis syndrome	TLS in the Pooled 3L+ DLBCL Treated Set was uncommon (reported in 0.6% subjects) and typically prevented by prophylactic measures administered in accord with local practice standards.

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
	Prophylactic TLS treatment has generally been successful in mitigating TLS risk when applied to DLBCL patients with high disease burden per local practice standards.
Cytopenia, including bone marrow failure	Prolonged cytopenia (laboratory assessments ≥ Grade 3 at Day 29) occurred in 36.2% of the targeted population, and can potentially impact benefit-risk since it could predispose patients to possible infections and bleeding. Risk management activities are routinely practiced by oncologists with careful surveillance of peripheral blood laboratory values, transfusions of platelets and red blood cells and growth factor administration as required.
Important potential risks	
Autoimmune disorders	The theoretical potential for an autoimmune reaction exists by means of anti-CD19 cross-reactivity with non-B-cell host tissues (molecular mimicry). Given that autoimmune disorders have not been reported to date in liso-cel-treated subjects, this risk remains theoretical.
Aggravation of graft versus host disease	There is a potential risk of aggravating pre-existing GvHD in patients with prior allo-HSCT. Subjects with acute or chronic GvHD were excluded from liso-cel clinical trials, and enrolled subjects had to be at least 3 months post allo-HSCT and be clinically stable prior to apheresis. Given the conventional practice of delaying transfusions and using irradiated filtered blood in patients with active GvHD, this risk remains theoretical.
Secondary malignancies/insertional oncogenesis	Secondary malignancies from insertional oncogenesis or otherwise remains a theoretical concern with all gene modified products, despite advances in self inactivating and non-replicating lentivectors and the absence of such cases with increasing experience using third generation gene modified effector cells. In reports of T-cell malignancies or other malignancies where a potential role for liso-cel transgene may be suspected, transgene assays will be performed and insertional site analysis also performed when appropriate, seeking evidence of clonality. In addition, population level epidemiologic analysis of specific malignancies by histologic type will be ongoing in post-marketing pharmacovigilance, the postauthorisation observational registry-based study BCM-005 (Section 3.2.1), and the post-clinical trial observational study GC-LTFU-001 (Section 3.2.3).
Cerebral oedema	Cerebral oedema has been observed with multiple products and product candidates in the field of CAR T therapeutics. At the time of the MAA, there has been a single report (0.3%) of Grade 2 right temporal brain oedema from a subject in the liso-cel Pooled 3L+ DLBCL Treated Set, after which the subject was subsequently determined to have DLBCL involvement of the CNS. In addition, a serious AE (SAE) of NT and cerebral oedema was reported from a paediatric B-cell acute lymphocytic leukaemia (B-ALL) subject enrolled in a liso-cel Phase 1 dose finding study who responded well to prompt therapy per the liso-cel treatment management guidelines. The liso-cel neurotoxicity treatment algorithm provides detailed guidance on cerebral oedema management if this potentially life-threatening condition occurs.
Generation of RCL	Using the current RCL assay, vesicular stomatitis virus glycoprotein envelope sequence has not been detected by quantitative polymerase chain reaction in liso-cel drug product or from peripheral blood of subjects post liso-cel therapy, indicating the absence of intact replicating virus in treated subjects. It is important to note that no instances of RCL generation during production or lentivirus mediated malignant transformation in animals or subjects have been reported. In the Pooled 3L+ DLBCL

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
	Treated Set, 359 subjects have been treated with liso-cel and no RCL has been detected. Therefore the risk of RCL with liso-cel treatment remains theoretical. Concern regarding possible RCL is driven by early experience with murine viral vectors for gene replacement therapy in patients who later developed leukaemia and led to the development of second and third generation modern vectors that are self-inactivating (SIN) and non-replicating. The concern (even with third generation vector) is that CAR transgene could indiscriminately transduce a site adjacent to an oncogene, mutate and potentially promote transformation and clonal proliferation. The latter has not been reported in animal or human studies, but the theoretical risk of transgene associated oncogenesis will be monitored as described above.
Immunogenicity	Liso-cel has the potential to induce immune response to its various components. This immune response could potentially cause allergic reactions such as anaphylaxis that require medical intervention. In addition, an immune response against liso-cel could theoretically reduce liso-cel efficacy by effector cell neutralisation or by promotion of more rapid clearance from circulation.
Transmission of infectious agents	Cells in solution could become contaminated with infectious agents during the liso-cel manufacturing process resulting in infection transfer during liso-cel infusion. However, tests for infectious agents (sterility, mycoplasma, etc.) are conducted at the end of the manufacturing process to eliminate this possibility. A single patient is known to have been treated with liso-cel product in which a slow growing *Staphylococcus epidermidis* was later detected during subsequent testing. In the absence of signs or symptoms of infection, and in an abundance of caution, the patient was treated with antibiotics and continued to have no evidence of infection thereafter. Human and animal derived materials are used in the liso-cel manufacturing process (eg, human serum albumin and foetal bovine serum). Although testing of the materials for contaminants is performed prior to use in the manufacturing process, it is not possible to completely eliminate the risk of infection arising from materials of biological origin. Subjects treated with liso-cel are immunocompromised from underlying disease and prior therapies, and almost all receive prophylactic antibiotics in accordance with local practice guidelines for bacterial, viral and fungal infections. All liso-cel treated patients should be carefully monitored for infection and appropriate treatment initiated if infection signs and symptoms are observed.
Reduced viability of liso-cel due to inappropriate product handling	Liso-cel must be manufactured, distributed, measured and administered at the correct dose with precise specifications per the approved product prescribing information and product handling information. Liso-cel cells can lose viability over time after thawing, and every effort must be taken to expedite administration after thawing. The total time from removal of liso-cel from frozen storage to patient administration should not exceed 2 hours. There have been no reports of mishandling at study sites through the end of the safety data reporting period.
Missing Information	
Impact on pregnancy and lactation	The theoretical risk for germline integration cannot be excluded; however, the absence of detectable replication-competent virus in drug product or in treated subjects suggests a negligible risk. It is not known whether liso-cel has the potential to be transferred to the foetus/child via the placenta or breastmilk that could cause toxicity, including B-cell

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
	lymphocytopenia superimposed on expected physiologic neonatal hypogammaglobulinaemia. Clinical trials have excluded pregnant and lactating female subjects; both male and female subjects of childbearing potential were required to use an effective method of contraception during treatment and thereafter because of the known teratogenicity of LDC. Pregnancy status for females of childbearing potential should be verified prior to treatment with liso-cel.
Long-term safety	The long-term follow-up (LTFU) safety study protocol (GC-LTFU-001) follows clinical trial subjects for up to 15 years and will provide monitoring for potential delayed new safety signals. In addition, postauthorisation registry-based study BCM-005 will further characterise the long-term safety profile of liso-cel in the post-marketing setting (Section 3.2.1).
Safety in patients < 18 years old	There is insufficient information available to determine the safety of liso-cel in patients < 18 years old. A liso-cel trial in paediatric subjects with B-cell malignancies is currently ongoing.
Safety in patients ≥ 75 years	Until 04-Apr-2022, the date of the initial marketing authorisation, there is limited information available to determine the safety of liso-cel in patients ≥ 75 years old. In the clinical study programme, 38 subjects aged ≥ 75 years old have been treated (24 males and 14 females).

2.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

There are no new safety concerns or reclassification of safety concerns in this updated RMP.

2.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Liso-cel clinical studies supporting the safety analyses in the RMP are listed in Table 2.3.1-1.

Clinical studies safety data is presented in 2 separate tables:

- Total Pooled 3L+ MCL and 2L+ FL and 2L/3L+ LBCL Treated Set includes safety data from time of liso-cel infusion for all studies.
- Single study BCM-003 liso-cel and SOC arm include safety data from date of randomization.

Risks are presented during different periods of treatment:

Treatment-emergent period:

Include AEs that started between the date of first dose and 90 days after the date of last infusion. For BCM-003, TEAEs are defined as AEs occurring or worsening on or after the date of randomization and within 90 days after last of chemotherapy (SOC Arm), or within 90 days after the infusion of liso-cel (liso-cel arm).

Post treatment-emergent period:

Selected risks are also presented by post treatment- emergent period, which starts from 91 days post the final infusion of liso-cel, or from initiation of another anticancer therapy or JCAR017 retreatment if subjects initiated another anticancer therapy or combination therapy (BCM-002) or JCAR017 retreatment prior to 91 days post the final cycle of JCAR017.

For BCM-003, 92 subjects were randomized to the liso-cel arm and 92 subjects were randomized to the SOC arm. Safety data for the Safety Analysis Set are presented for 183 subjects from time of randomization (92 and 91 subjects in the liso-cel and SOC arms, respectively). In the SOC arm, 1 subject withdrew consent before starting SOC treatment and was excluded from the Safety Set treated analysis. Of the 92 subjects randomized to the liso-cel arm, safety data are presented from the time of infusion for the 89 subjects that received liso-cel. The below 3 subjects were excluded from the liso-cel treated analysis:

- One subject received nonconforming product.
- One subject was randomized but withdrew consent before receiving liso-cel due to rapid progression before liso-cel infusion.
- One subject was randomized but never received liso-cel; the subject discontinued from treatment on Day 26 due to study drug manufacturing failure.

In BCM-003, the overall incidences of AEs, TEAEs, and deaths for subjects in the liso-cel arm were similar to that for subjects in the SOC arm, however the AE profiles were different consistent with respective MOAs of liso-cel and immunochemotherapy.

Summarized information on the liso-cel post-marketing experience is included in selected risks.

The important identified and potential risks as well as missing information are listed below.

Important Identified Risks

- Cytokine release syndrome (see Table 2.7.3.1-1)
- Neurologic toxicity including ICANS (see Table 2.7.3.1-2)
- Infections (see Table 2.7.3.1-3)
- Hypogammaglobulinaemia (see Table 2.7.3.1-4)
- Macrophage activation syndrome/haemophagocytic lymphohistiocytosis (see Table 2.7.3.1-5)
- Tumour lysis syndrome (see Table 2.7.3.1-6)
- Cytopenia, including bone marrow failure (see Table 2.7.3.1-7)
- Secondary malignancy of T-cell origin (see Table 2.7.3.1-8)

Important Potential Risks

- Autoimmune disorders (see Table 2.7.3.1-9)
- Aggravation of graft versus host disease (see Table 2.7.3.1-10)
- Secondary malignancies (except secondary malignancy of T-cell origin) (see Table 2.7.3.1-11)
- Generation of replication competent lentivirus (see Table 2.7.3.1-12)
- Immunogenicity (see Table 2.7.3.1-13)

- Transmission of infectious agents (see Table 2.7.3.1-14)
- Reduced viability of liso-cel due to inappropriate product handling (see Table 2.7.3.1-15)

Missing Information

- Impact on pregnancy and lactation (see Table 2.7.3.2-1)
- Long-term safety (see Table 2.7.3.2-1)
- Safety in patients < 18 years old (see Table 2.7.3.2-1)
- Safety in patients ≥ 75 years (see Table 2.7.3.2-1)

2.7.3.1 Presentation of Important Identified and Important Potential Risks

Table 2.7.3.1-1: Important Identified Risk: Cytokine Release Syndrome

Important Identified Risk: Cytokine Release Syndrome	
Potential mechanisms	Cytokine release syndrome is a non–antigen-specific toxicity that occurs in association with high-level immune activation resulting in elevated inflammatory cytokines. Cytokine release syndrome clinically manifests when large numbers of lymphocytes (eg, B-cells, T-cells, and/or natural killer cells) and/or myeloid cells (eg, macrophages, dendritic cells, and monocytes) become activated and release inflammatory cytokines.[92] Higher disease burden and higher baseline levels of inflammatory cytokines are associated with higher incidence of CRS.[93,94,95]
Evidence source and strength of evidence	Cytokine release syndrome has been reported with all anti-CD19 directed CAR T therapeutics and is considered intrinsic to the therapeutic class. In the 3L+ MCL Treated Set, 61.4% of subjects experienced CRS. 34.1% of the events were mild and 26.1% of the events were moderate in severity. No events were severe and 1.1% were reported being life-threatening in severity. In the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set, 46.4% of subjects experienced CRS. 29.4% of events were mild and 15.5% of the events were moderate in severity. 7 (0.8%) of the events were severe and 5 (0.6%) events were life-threatening in severity. Cytokine release syndrome is considered an important identified risk as it requires careful monitoring and prompt intervention to minimise the potential for life-threatening or even fatal outcomes. Further evaluation of CRS frequency, severity, and potential risk factors will be conducted in the post-marketing setting with an observational registry-based study BCM-005 including patients followed for up to 15 years as applicable.
Characterization of risk	**Frequency with 95% CI** In the 3L+ MCL Treated Set, 61.4% of subjects experienced CRS. In the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set, 46.4% of subjects experienced CRS.

Table 2.7.3.1-1: Important Identified Risk: Cytokine Release Syndrome

Important Identified Risk: Cytokine Release Syndrome

CRS from time of infusion	**3L+ MCL**	**2L+ FL**	**LBCL**			**Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL**
	017001 MCL Cohort	**FOL-001**	**2L LBCL Total**	**3L+ LBCL Total**	**Total LBCL**	**Total Pooled**
Total number of subjects; n	88	130	177	431	608	826
Subjects with ≥ 1 AE; n	54	75	80	174	254	383
Grade 3 or 4; n (%)	1 (1.1)	1 (0.8)	2 (1.1)	8 (1.9)	10 (1.6)	12 (1.5)
Grade 5; n (%)	0	0	0	0	0	0
Subjects with ≥ 1 SAE; n (%)	21 (23.9)	12 (9.2)	21 (11.9)	79 (18.3)	100 (16.4)	133 (16.1)
Not Recovered/ Not Resolved; n (%)	1 (1.1)	0	0	4 (0.9)	4 (0.7)	5 (0.6)
Recovered/ Resolved; n (%)	20 (22.7)	12 (9.2)	21 (11.9)	75 (14.4)	96 (15.8)	128 (15.5)
Incidence (%) of subjects with ≥ 1 AE (95% CI)	61.4 (50.4, 71.6)	57.7 (48.7, 66.3)	45.2 (37.7, 52.8)	40.4 (35.7, 45.2)	41.8 (37.8, 45.8)	46.4 (42.9, 49.8)

Table 2.7.3.1-1: Important Identified Risk: Cytokine Release Syndrome

Important Identified Risk: Cytokine Release Syndrome

CRS from time of randomization	Study BCM-003	
	Liso-cel Arm	SOC Arm
Total number of subjects; n	92	91
Subjects with ≥ 1 AE; n	45	0
Grade 3 or 4; n (%)	1 (1.1)	0
Grade 5; n (%)	0	0
Subjects with ≥ 1 SAE; n (%)	12 (13.0)	0
Not Recovered/ Not Resolved; n (%)	1 (1.1)	0
Recovered/ Resolved; n (%)	11 (12.0)	0
Incidence (%) of subjects with ≥ 1 AE (95% CI)	48.9 (38.3, 59.6)	0 (0.0, 4.0)

Seriousness/Outcomes

In the 3L+ MCL Treated Set and the 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set, serious CRS events were reported in 21 and 133 subjects (respectively); the CRS category included only the PT of Cytokine Release Syndrome.

Severity and Nature of Risk

No Grade 5 CRS events were reported in the Total 3L+ MCL,2L+ FL and 2L/3L+ LBCL Pooled Set.

Risk factors and risk groups

Disease burden is a risk factor for LBCL patients for the important identified risk of CRS. Analysis of AEs by Baseline Disease Characteristic showed that greater disease burden (ie, SPD ≥ 50 cm^2 by computed tomography [CT] scan or lactate dehydrogenase [LDH] ≥ 500 U/L), or baseline inflammatory state (ie, C-reactive protein [CRP] ≥ 20 mg/L) were associated with higher rates of all-grade CRS. Early onset of CRS usually predicts more severe manifestations. Patients with greater DLBCL disease burden (higher SPD and/or LDH) or who have elevated baseline levels of inflammatory marker (CRP), are more likely to develop CRS. Overall, in the Pooled 2L Treated Set and the Pooled 3L+ LBCL Treated Sets, CRS was more

Table 2.7.3.1-1: Important Identified Risk: Cytokine Release Syndrome

Important Identified Risk: Cytokine Release Syndrome	
	frequent in subjects with higher disease burden (SPD ≥ 50 cm^2) or with more aggressive disease (HGBCL or subjects who required bridging chemotherapy). Disease burden is a risk factor for FL patients for the important identified risks of CRS. In 3L+ FL, the frequency of CRS was higher in subjects with SPD ≥ 50 cm^2 (greater disease burden) than SPD < 50 cm^2, although a small sample size for SPD ≥ 50 cm^2 subgroup (n=24) limits the interpretability of this difference. Disease burden does not seem to be a risk factor for MCL patients for the important identified risk of CRS. In 3L+ MCL, the overall frequency and severity of CRS was generally similar also between subjects with pre-LDC SPD < 50 cm^2 (n=73) and those with pre-LDC SPD ≥ 50 cm^2 (n=7), but the small sample size of the second group limits the interpretability of the results.
Preventability	Patients with greater disease burden (higher SPD and/or LDH) and greater inflammatory state (higher CRP) require close monitoring. Detailed guidance on the identification, monitoring, grading, and management of CRS will be included in the approved product label to prevent severe CRS-related toxicities. HCPs will be provided with guidance in the prescribing information and the educational tools on the appropriate patient monitoring after the liso-cel infusion. A CRS management algorithm has been developed on the use of tocilizumab and corticosteroids for the management of toxicity related to CRS and is included in Section 4.4 (Special warnings and precautions for use) of the SmPC. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, suitable alternative measures instead of tocilizumab for the management of toxicity related to CRS can be used. Education of HCPs enables detection and management of CRS for all patients at an early stage that can mitigate potentially serious outcomes. As part of the RMP, HCPs who are expected to prescribe, dispense, and administer liso-cel will receive educational tools on identification and management of CRS.
Impact on the risk-benefit balance of the product	Cytokine release syndrome can have mild to life-threatening or even fatal impact. Severe and life-threatening manifestations of CRS include cardiac toxicity, respiratory distress with hypoxia, renal injury, hepatic failure and disseminated intravascular coagulation.[92] Fatal cases of CRS have not been reported in the liso-cel Development Programme. Cytokine release syndrome was ongoing at the time of death for 4 subjects in the Pooled 3L+ DLBCL Set who did not have resolution of CRS; however, CRS was not the cause of death for any of these subjects.
Public health impact	Cytokine release syndrome occurs mainly after bispecific T-cell engaging and CAR T-cell therapy, with an incidence ranging from 2% to 94%, reflecting variation in product properties, variable doses, and variable CRS definitions. Isolated cases of CRS have been related to recombinant cytokine therapies such as IL-2, HSCT, and even conventional chemotherapy and radiotherapy.[96] Based on the available data for liso-cel with the majority of CRS events being mild to moderate in severity and given that liso-cel will be administered in a controlled distribution setting together with HCP and patient educational programs as additional risk minimisation measures, it appears likely that this risk can be managed safely, which suggests a limited impact on public health.
MedDRA terms	See Annex 7

Table 2.7.3.1-2: Important Identified Risk: Neurologic Toxicity including ICANS

Important Identified Risk: Neurologic Toxicity including ICANS	
Potential mechanisms	CAR T-cell associated NT is highly variable and may manifest as encephalopathy, aphasia, delirium, difficulty concentrating, agitation, tremor, and seizures. As headache is very common in patients who have not undergone CAR T-cell therapy it may be present but not represent CAR T-cell associated NT. Neurologic symptoms may occur during, or more commonly after, CRS but may also occur in isolation. The American Society for Transplantation and Cellular Therapy (ASTCT) proposed a consensus grading system that introduced the definition "immune effector cell–associated neurotoxicity syndrome" (ICANS). ICANS may have features that overlap with other encephalopathies but has the more specific characteristic of an awake patient who is mute and does not respond verbally or physically to an examiner. ICANS may have a unique pathophysiology compared with other encephalopathies.[97] Bonifant et al[98] suggested that elevated cytokine levels were responsible for such events, but also implicated direct CAR T-cell effects on the CNS. Elevated levels of IL-6 have been considered important in NT pathophysiology, but NT has been observed in subjects for whom IL-6 is not the primarily elevated cytokine and in whom no CRS occurs. Another report found elevated levels of the excitatory NMDA receptor agonists glutamate and quinolinic acid in cerebrospinal fluid from patients with neurotoxicity.[99] Patients and animals with severe NT have had evidence of endothelial activation and increased blood brain barrier permeability.[100] Diffuse cerebral oedema has been reported after treatment with both investigational and approved CAR T-cell therapeutics, sometimes following seizures but more often with fulminant onset and few antecedent clinical warning signs, suggesting that it may have a pathophysiology distinct from other NT. It may manifest with decerebrate or decorticate posturing, papilledema, hypoventilation, bradycardia, systolic hypertension and diffuse cerebral oedema apparent on neuroimaging. Bonifant et al[98] suggested that elevated cytokine levels were responsible for such events, but also implicated direct CAR T-cell effects on the CNS. The pathobiology of cerebral oedema associated with CAR T therapy has not been established. However, histological and neuroimaging evidence supports cerebral vasogenic oedema triggered by cytokine-mediated blood brain barrier (BBB) dysfunction as the underlying pathobiological mechanism. Studies have identified the higher peak in vivo proliferation of CAR T-cells, higher cell doses, conditioning chemotherapy, ALL rather than NHL, and higher burden of disease as a few of the important risk factors for neurotoxicity.[101]
Evidence source and strength of evidence	Neurologic toxicity including ICANS is an important identified risk due to its seriousness and potential for associated disability, including death, if left untreated. In addition to CRS, NT is an expected AE associated with CAR T-cell therapy.[102] The diagnosis is based on characteristic clinical signs and symptoms following CAR T infusion. Neurologic toxicities are primarily managed with supportive care for low grade toxicity, and corticosteroids for more severe NT.[36] As investigators were trained in the recognition and management of NT, the liso-cel clinical studies used the investigator's judgment to prospectively identify all treatment-emergent AEs (TEAEs) considered to be NT related to liso-cel and termed this finding iiNT. The maximum iiNT grade was determined by the highest grade of any component TEAE considered part of iiNT. In the 3L+ MCL Treated Set, 30.7% of subjects experienced iiNT. 11.4% were mild and 1.5% of the events were moderate in severity. 3.1% of the events were severe and 1.1% were life-threatening in severity with none being fatal. In the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL

Table 2.7.3.1-2: Important Identified Risk: Neurologic Toxicity including ICANS

Important Identified Risk: Neurologic Toxicity including ICANS

Pooled Set, 24.1% of subjects experienced iiNT. 9.3% were mild and 7.1% of the events were moderate in severity. 6.7% of the events were severe and 1.0% were life-threatening in severity with none being fatal. No subjects had Grade 5 iiNT but some liso-cel treated subjects had ongoing iiNT at the time of death from other causes.

In the 3L+ MCL Treated Set, no subjects reported events of cerebral oedema. In the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set, there is one reported case of cerebral oedema in the context of iiNT- a localised, unilateral, Grade 2 right temporal oedema reported in a subject who was later determined to have DLBCL involvement of the CNS. In the post-marketing setting, there have been reports of cerebral oedema in the context of neurotoxicity in patients infused with liso-cel in whom an association between cerebral oedema and liso-cel infusion could not be excluded. Serious and life-threatening reports of cerebral oedema have been reported after treatment with other CAR T products and CAR T product candidates.

Characterization of risk

Frequency with 95% CI

In the 3L+ MCL Treated Set, 30.7% of subjects experienced iiNT, none of which reported cerebral oedema. In the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set, 24.1% of subjects experienced iiNT with one reported case of cerebral oedema in 3L+ LBCL in Study 017001 in the context of iiNT (a localised, unilateral, Grade 2 right temporal oedema was reported in a subject who was later determined to have DLBCL involvement of the CNS).

iiNT from time of infusion	**3L+ MCL**	**2L+ FL**	**LBCL**			**Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL**
	017001 MCL Cohort	**FOL-001**	**2L LBCL Total**	**3L+ LBCL Total**	**Total LBCL**	**Total Pooled**
Total number of subjects; n	88	130	177	431	608	826
Subjects with ≥ 1 AE; n	27	21	32	119	151	199[a]
Grade 3 or 4; n (%)	8 (9.1)	4 (3.1)	8 (4.5)	43 (10.0)	51 (8.4)	63 (7.6)
Grade 5; n (%)	0	0	0	0	0	0
Subjects with ≥ 1 SAE; n (%)	11 (12.5)	7 (5.4)	8 (4.5)	68 (15.8)	76 (12.5)	94 (11.4)
Not Recovered/ Not Resolved; n (%)	0	0	0	5 (1.2)	5 (0.8)	5 (0.6)

Table 2.7.3.1-2: Important Identified Risk: Neurologic Toxicity including ICANS

Important Identified Risk: Neurologic Toxicity including ICANS

Recovering / Resolving; n (%)	1 (1.1)	0	0	2 (0.5)	2 (0.3)	3 (0.4)
Recovered/ Resolved; n (%)	10 (11.4)	7 (5.4)	8 (4.5)	61 (14.2)	69 (11.3)	86 (10.4)
Incidence (%) of subjects with ≥ 1 AE (95% CI)	30.7 (21.3, 41.4)	16.2 (10.3, 23.6)	18.1 (12.7, 24.6)	27.6 (23.4, 32.1)	24.8 (21.4, 28.5)	24.1 (21.2, 27.2)

[a] Includes a case of a localised, unilateral, Grade 2 right temporal lobe oedema which was reported in one subject in Study 017001.

iiNT from time of randomization	**Study BCM-003**	
	Liso-cel Arm	**SOC Arm**
Total number of subjects; n	92	91
Subjects with ≥ 1 AE; n	10	0
Grade 3 or 4; n (%)	4 (4.3)	0
Grade 5; n (%)	0	0
Subjects with ≥ 1 SAE; n (%)	3 (3.3)	0
Not Recovered/ Not Resolved; n (%)	1 (1.1)	0
Recovering/ Resolving; n (%)	0	0
Recovered/ Resolved; n (%)	2 (2.2)	0
Incidence (%) of subjects	10.9 (5.3, 19.1)	0 (0.0, 4.0)

Table 2.7.3.1-2: Important Identified Risk: Neurologic Toxicity including ICANS

Important Identified Risk: Neurologic Toxicity including ICANS			
	with ≥ 1 AE (95% CI)		

Seriousness/Outcomes

In the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set, serious iiNT events reported with an overall frequency of greater than 2% included the PTs of confusional state (25 subjects), aphasia (23 subjects), encephalopathy (19 subjects), and tremor (17 subjects).

Severity and Nature of Risk

No Grade 5 iiNT events were reported in the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set.

Risk factors and risk groups

Disease burden is a risk factor for LBCL patients for the important identified risk of NT. Analysis of AEs by Baseline Disease Characteristic showed that greater disease burden (ie, SPD ≥ 50 cm2 by CT scan or LDH ≥ 500 U/L), or baseline inflammatory state (ie, CRP ≥ 20 mg/L) were associated with higher rates of all grade iiNT-. Overall, in the Pooled 2L Treated Set and the Pooled 3L+ LBCL Treated Sets, iiNT was more frequent in subjects with higher disease burden (SPD ≥ 50 cm^2) or with more aggressive disease (HGBCL or subjects who required bridging chemotherapy). Pre-existing secondary CNS lymphoma extension of DLBCL to the CNS does not appear to be associated with a greater risk for cerebral oedema in the context of ICANS.

Disease burden is not a risk factor for FL patients for the important identified risk of NT. In 3L+ FL, the frequency of NT was the same regardless of the disease burden (ie, SPD ≥ 50 cm^2). Analysis of AEs by baseline inflammatory state (ie, CRP ≥ 20 mg/L) showed no differences in the frequency or severity of iiNT.

Disease burden does not seem to be a risk factor for MCL patients for the important identified risk of NT. In 3L+ MCL, the overall frequency and severity of iiNT was generally similar (< 20% difference) in subjects with LDH ≥ ULN (n=41) and those with LDH < ULN (n=47).

Preventability

Health care prescribers will be provided with NT recognition, management and iiNT treatment guidance through the receipt of educational tools and in the prescribing information. This guidance includes information on early detection, management and aggressive intervention for cerebral oedema. Patients will be counselled to seek immediate medical attention should signs or symptoms of NT occur at any time.

Patients with greater disease burden (higher SPD and/or LDH) and greater inflammatory state (higher CRP) require close monitoring as these clinical features suggest greater risk for the development of NT. However, all liso-cel patients require close monitoring post infusion, and the CRS and NT treatment guidelines should appropriately adjust for more rapid or more severe onset of NT clinical features.

HCPs are provided with guidance in the prescribing information and the educational tools on the adequate patient monitoring after liso-cel infusion. Physicians should consider hospitalisation at the first signs or symptoms of suspected NT.

Treatment of cerebral oedema can include neurology consultation, transfer to intensive care for supportive care and careful monitoring, neuroimaging, electroencephalogram, intubation for airway protection, levetiracetam anti-seizure prophylaxis, high dose corticosteroids, hyperventilation, hypertonic saline or mannitol, IL-6 antagonists, IL-1 antagonists and high dose cyclophosphamide.

Table 2.7.3.1-2: Important Identified Risk: Neurologic Toxicity including ICANS

Important Identified Risk: Neurologic Toxicity including ICANS	
	As a part of the RMP, HCPs who are expected to prescribe, dispense, and administer liso-cel will receive educational tools on identification and management of NT.
Impact on the risk-benefit balance of the product	Neurologic toxicity including ICANS is considered as an important identified risk due to its seriousness, and potential for associated disability, including death if left untreated. Cerebral oedema is considered one of the most important identified risks associated with CAR T therapy, because it can be sudden in onset and rapidly evolve to fatal disease when untreated.
Public health impact	CAR T-cell therapy is an approved therapy for patients with refractory paediatric B-ALL and R/R DLBCL. NT can occur in up to 87% of patients treated with some CAR T-cell therapeutics depending on the patient population treated, the therapeutic target and the product employed. Signs and symptoms are highly variable and can include encephalopathy, aphasia, delirium, dizziness, and seizures. Almost all NT is reversible. While Grade 1 NT may only require supportive care with prophylactic levitiracetam, NT may progress rapidly and may require close monitoring, neurologist consultation, neuroimaging and escalating doses of corticosteroids. For patients with severe or higher (Grade 3 to 4) NT, monitoring in the intensive care unit is recommended[103] with respiratory support and consideration of intubation for airway protection. The infrequent nature of cerebral oedema with the experience to date suggests that the public health impact is low and the possibility of cerebral oedema should not deter providers from using liso-cel therapy in appropriately selected LBCL patients.
MedDRA terms	See Annex 7

Table 2.7.3.1-3: Important Identified Risk: Infections

Important Identified Risk: Infections	
Potential mechanisms	Cytopenia and hypogammaglobulinaemia predispose patients to infections, and result from conditioning LDC and B-cell depleting liso-cel therapy.
Evidence source and strength of evidence	In addition to the known risk of infection from the LDC with fludarabine and cyclophosphamide, liso-cel can cause depletion of B-cells and increase a patients' risk for developing high grade and serious infections. In the 3L+ MCL Treated Set, 14.8% of subjects experienced ≥ Grade 3 treatment-emergent infections. 11.4% were severe and 1.1% of the events were lifethreatening- in severity with 2.3% of the events being fatal. In the Total 3L+ MCL, 2L+FL and 2L/3L+ LBCL Pooled Set, 11.3% of liso-cel treated subjects had ≥ Grade 3 treatment-emergent infections. 8.5% were severe and 1.7% of the events were life-threatening in severity with 1.1% of the events being fatal.
Characterization of risk	**Frequency with 95% CI** In the 3L+ MCL Treated Set, and in the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set, 14.8%, and 11.3% of subjects experienced ≥ Grade 3 treatment-emergent infections, respectively.

Table 2.7.3.1-3: Important Identified Risk: Infections

Important Identified Risk: Infections

Grade 3 or Higher Infections from time of infusion	3L+ MCL	2L+ FL	LBCL			Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL
	017001 MCL Cohort	FOL-001	2L LBCL Total	3L+ LBCL Total	Total LBCL	Total Pooled
Total number of subjects; n	88	130	177	431	608	826
Subjects with ≥ 1 AE; n	13	7	18	55	73	93
Grade 3 or 4; n (%)	13 (14.8)	7 (5.4)	18 (10.2)	55 (12.8)	73 (12.0)	93 (11.3)
Grade 5; n (%)	2 (2.3)	0	2 (1.1)	5 (1.2)	7 (1.2)	9 (1.1)
Subjects with ≥ 1 SAE; n (%)	8 (9.1)	6 (4.6)	11 (6.2)	36 (8.4)	47 (7.7)	61 (7.4)
Not Recovered / Not Resolved; n (%)	2 (2.3)	0	0	7 (1.6)	7 (1.2)	9 (1.1)
Recovered /Resolved with Sequalae; n (%)	0	0	0	1 (0.2)	1 (0.2)	1 (0.1)
Recovered / Resolved; n (%)	4 (4.5)	6 (4.6)	9 (5.1)	23 (5.3)	32 (5.3)	42 (5.1)
Fatal; n (%)	2 (2.3)	0	2 (1.1)	5 (1.2)	7 (1.2)	9 (1.1)
Incidence (%) of subjects with ≥ 1 AE (95% CI)	14.8 (8.1, 23.9)	5.4 (2.2, 10.8)	10.2 (6.1, 15.6)	12.8 (9.8, 16.3)	12.0 (9.5, 14.9)	11.3 (9.2, 13.6)

Table 2.7.3.1-3: Important Identified Risk: Infections

Important Identified Risk: Infections

Grade 3 or Higher Infections from time of randomization	**Study BCM-003**	
	Liso-cel Arm	**SOC Arm**
Total number of subjects; n	92	91
Subjects with ≥ 1 AE; n	14	19
Grade 3 or 4; n (%)	14 (15.2)	19 (20.9)
Grade 5; n (%)	0	1 (1.1)
Subjects with ≥ 1 SAE; n (%)	10 (10.9)	13 (14.3)
Not Recovered/ Not Resolved; n (%)	0	2 (2.2)
Recovered/ Resolved With Sequelae; n (%)	0	0
Recovered/ Resolved; n (%)	10 (10.9)	10 (11.0)
Incidence (%) of subjects with ≥ 1 AE (95% CI)	15.2 (8.6, 24.2)	20.9 (13.1, 30.7)

Seriousness/Outcomes

In the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set, serious Grade 3 or higher events of infection were reported in 61 subjects. PTs reported in ≥ 2 subjects included Pneumonia (12 subjects), Sepsis (9 subjects), Septic shock, COVID-19, and Upper respiratory tract infection (4 subjects each), COVID-19 pneumonia (3 subjects), Bacteraemia, Streptococcal bacteraemia, Bacterial sepsis, Candida sepsis, and Urinary tract infection (2 subjects each).

Severity and Nature of Risk

Table 2.7.3.1-3: Important Identified Risk: Infections

Important Identified Risk: Infections	
	In the 3L+ MCL Treated Set, 2 Grade 5 events were reported (PTs were COVID-19 pneumonia and Cryptococcal meningoencephalitis). In the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set, PTs reported in the Grade 5 events included COVID-19, COVID-19 pneumonia, Candida sepsis, Cryptococcal meningoencephalitis, pneumonia, progressive multifocal leukoencephalopathy, septic shock, and Staphylococcal sepsis (1 subject each).
Risk factors and risk groups	There was a numerically higher percentage of subjects with Grade ≥ 3 infection in those with Grade ≥ 3 neutropenia prior to LDC (23.%) than in those who had Grade ≤ 2 neutropenia prior to LDC (11.5%) in Study 017001.
Preventability	A high index of suspicion is warranted in the event of prolonged or recurrent cytopenia, especially in conjunction with hypogammaglobulinaemia, severe lymphopenia, severe neutropenia or febrile neutropenia and/or recent use of corticosteroids. Patients receiving CD19 CAR T-cell therapy for relapsed/refractory lymphoma experience prolonged and profound B-cell aplasia and hypogammaglobulinemia, placing them at a higher risk for severe COVID-19. Despite attenuated humoral response to mRNA-based vaccines, patients demonstrate normal or heightened functional T-cell responses, including antiviral T-cell activity against SARS-CoV-2 variants.[104,105] Prescribers are encouraged to closely monitor patients for signs and symptoms of infection, to counsel their patients on the importance of prevention measures for COVID-19, and consider use of prophylactic antiviral, antibacterial, and antifungal therapies in accordance with local practice standards or guidelines.
Impact on the risk-benefit balance of the product	Infection is considered an important identified risk due to the potential for life-threatening or even fatal outcomes in this patient population. Additional evaluation of the frequency, severity, seriousness and predictors of post-marketing infections is planned for study in the postauthorisation observational registry-based study BCM005, the post trial long-term follow-up study (GC-LTFU-001) and spontaneous AE reports.
Public health impact	Serious infections are common in immunocompromised patients afflicted with advanced hematologic malignancies, with both antibiotic responsive organisms and sometimes treatment resistant infections especially after hospital care and prior antibiotic therapy. Effective treatment requires coordination of antimicrobial use between regional clinics and hospitals, and aggressive early infection characterisation. Impaired immunity, however, may still result in poor treatment responses and outcomes.[106]
MedDRA terms	See Annex 7

Table 2.7.3.1-4: Important Identified Risk: Hypogammaglobulinaemia

Important Identified Risk: Hypogammaglobulinaemia	
Potential mechanisms	Hypogammaglobulinaemia is caused by prolonged B-cell depletion.
Evidence source and strength of evidence	Hypogammaglobulinaemia is caused by B-cell aplasia. It is an on target anti-CD19 effect consistent with the liso-cel mechanism of action (MOA), as well as a known risk from prior treatment with rituximab and other drugs that can promote lymphopenia, including LDC with fludarabine and cyclophosphamide.

Table 2.7.3.1-4: Important Identified Risk: Hypogammaglobulinaemia

Important Identified Risk: Hypogammaglobulinaemia

In the 3L+ MCL Treated Set, TEAEs of hypogammaglobulinaemia were noted in 6.8% of subjects in the treatment-emergent period and in 4.9% of subjects in the post treatment-emergent period. Grade ≥ 3 hypogammaglobulinaemia was not reported in any subjects in the treatment-emergent period or in the post treatment-emergent period.

In the Total Pooled 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Treated Set, TEAEs of hypogammaglobulinaemia were noted in 9.2% of subjects in the treatmentemergent- period and in 4.4% of subjects in the post treatment-emergent period. Grade ≥ 3 hypogammaglobulinaemia was reported in 0.1% of subjects in the treatment-emergent period and was reported in 0.1% of subjects in the post treatmentemergent- period.

Characterization of risk

Frequency with 95% CI

In the 2L+ FL Treated Set, 3.8% of subjects experienced hypogammaglobulinaemia. 2.3% of the events were mild and 1.5% of the events were moderate in severity. In the 3L+ MCL Treated Set, 6.8% of subjects experienced hypogammaglobulinaemia. 1.1% of the events were mild and 5.7% of the events were moderate in severity.

In the Total Pooled 3L+ MCL and 2L+ FL and 2L/3L+ LBCL Treated Set, 9.2% of subjects experienced hypogammaglobulinaemia. 2.7% of events were mild, 5.7% of the events were moderate, and 0.1% of the events were severe in severity. No fatal events were reported.

Hypogammaglobulinaemia from time of infusion	**3L+ MCL**	**2L+ FL**	**LBCL**			**Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL**
	017001 MCL Cohort	**FOL-001**	**2L LBCL Total**	**3L+ LBCL Total**	**Total LBCL**	**Total Pooled**
Treatment-emergent period						
Total number of subjects; n	88	130	177	431	608	826
Subjects with ≥ 1 AE; n	6	5	12	53	65	76
Grade 3 or 4; n (%)	0	0	1 (0.6)	0	1 (0.2)	1 (0.1)
Grade 5; n (%)	0	0	0	0	0	0
Subjects with ≥ 1 SAE; n (%)	0	0	0	0	0	0

Table 2.7.3.1-4: Important Identified Risk: Hypogammaglobulinaemia

Important Identified Risk: Hypogammaglobulinaemia

Incidence (%) of subjects with ≥ 1 AE (95% CI)	6.8 (2.5, 14.3)	3.8 (1.3, 8.7)	6.8 (3.6, 11.5)	12.3 (9.3, 15.8)	10.7 (8.3, 13.4)	9.2 (7.3, 11.4)
Post-treatment emergent period						
Total number of subjects; n	82	129	167	392	559	770
All AEs; n (%)	4 (4.9)	3 (2.3)	4 (2.4)	23 (5.9)	27 (4.8)	34 (4.4)
Grade 3 or 4; n (%)	0	1 (0.8)	0	0	0	1 (0.1)

Hypogammaglobulinaemia from time of randomization	**Study BCM-003**	
	Liso-cel Arm	**SOC Arm**
Treatment-emergent period		
Total number of subjects; n	92	91
Subjects with ≥ 1 AE; n	10	3
Grade 3 or 4; n (%)	1 (1.1)	0
Subjects with ≥ 1 SAE; n (%)	0	0
Incidence (%) of subjects with ≥ 1 AE (95% CI)	10.9 (5.3, 19.1)	3.3 (0.7, 9.3)
Post-treatment emergent period		
Total number of subject; ns	92	91
All AEs; n (%)	0	0
Grade 3 or 4; n (%)	0	0

Seriousness/Outcomes

Table 2.7.3.1-4: Important Identified Risk: Hypogammaglobulinaemia

Important Identified Risk: Hypogammaglobulinaemia	
	No serious hypogammaglobulinaemia events were reported in the 3L+ MCL Treated Set, and in the Total Pooled 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Treated Set during the treatment emergent period. No serious hypogammaglobulinaemia events were reported in the 3L+ MCL treated set. One serious hypogammaglobulinaemia event was reported in one subject in the Total Pooled 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Treated Set (PT of hypogammaglobulinaemia) in the post treatment-emergent period. The outcome of the SAE was reported to be not recovered/not resolved. **Severity and Nature of Risk** There were no Grade 5 hypogammaglobulinaemia events in the 3L+ MCL Treated Set, and in the Total Pooled 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Treated Set.
Risk factors and risk groups	Prior treatment with rituximab and other drugs that can promote lymphopenia.
Preventability	Immunoglobulin levels should be monitored after treatment with liso-cel and hypogammaglobulinaemia managed using infection precautions, antibiotic prophylaxis, and/or immunoglobulin replacement in accordance with local guidelines.
Impact on the risk-benefit balance of the product	Hypogammaglobulinaemia makes patients susceptible to potentially life-threatening infections and is therefore considered an important identified risk.
Public health impact	Hypogammaglobulinaemia can be secondary to malignancies that affect immunoglobulin production, such as chronic lymphocytic leukaemia, multiple myeloma and B-cell lymphomas. Immunodeficiency can also be secondary to prior treatment for the patient's underlying malignancy.[107] Symptomatic hypogammaglobulinaemia is defined as 2 or more non-neutropenic infections within 6 months of medication administration and requiring IV immunoglobulin treatment. Serially measuring immunoglobulin levels (IgG, IgA and IgM) can be helpful to identify high-risk patients for developing symptomatic hypogammaglobulinaemia.[108]
MedDRA terms	See Annex 7

Table 2.7.3.1-5: Important Identified Risk: Macrophage Activation Syndrome/Haemophagocytic Lymphohistiocytosis

Important Identified Risk: Macrophage Activation Syndrome/Haemophagocytic Lymphohistiocytosis	
Potential mechanisms	Macrophage activation syndrome may be part of the continuum of dysregulated inflammatory responses including CSR, lymphohistiocytic tissue infiltration, and multiorgan dysfunction. Cytokine release syndrome and infections, in particular infections mainly of viral origin but also but also induced bacterial, protozoal, or mycotic infection, may be immune triggers leading to MAS/HLH.
Evidence source and strength of evidence	In the 3L+ MCL Treated set, no subjects experienced a MAS/HLH event. In the Total Pooled 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Treated Set, 0.6% of subjects experienced MAS/HLH events. 0.1% of events were moderate and 0.2% of the events were life-threatening in severity. 0.2% of the events were fatal.

Table 2.7.3.1-5: Important Identified Risk: Macrophage Activation Syndrome/Haemophagocytic Lymphohistiocytosis

Important Identified Risk: Macrophage Activation Syndrome/Haemophagocytic Lymphohistiocytosis

Macrophage activation syndrome/HLH has been reported in association with approved CD19-directed CAR T-cell therapies.

Characterization of risk

Frequency with 95% CI

In the 3L+ MCL Treated set, no subjects experienced a MAS/HLH event. In the Total Pooled 3L+ MCL and 2L+ FL and 2L/3L+ LBCL Treated Set 0.6% of subjects experienced MAS/HLH events.

MAS/HLH from time of infusion	**3L+ MCL**	**2L+ FL**	**LBCL**			**Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL**
	017001 MCL Cohort	**FOL-001**	**2L LBCL Total**	**3L+ LBCL Total**	**Total LBCL**	**Total Pooled**
Total number of subjects; n	88	130	177	431	608	826
Subjects with ≥ 1 AE; n	0	1	2	2	4	5
Grade 3 or 4; n (%)	0	1 (0.8)	1 (0.6)	2 (0.5)	3 (0.5)	4 (0.5)
Grade 5; n (%)	0	1 (0.8)	1 (0.6)	0	1 (0.2)	2 (0.2)
Subjects with ≥ 1 SAE; n (%)	0	1 (0.8)	1 (0.6)	2 (0.5)	3 (0.5)	4 (0.5)
Not Recovered/ Not Resolved; n (%)	0	0	0	2 (0.5)	2 (0.3)	2 (0.2)
Fatal; n (%)	0	1 (0.8)	1 (0.6)	0	1 (0.2)	2 (0.2)
Incidence (%) of subjects with ≥ 1 AE (95% CI)	0 (0.0, 4.1)	0.8 (0.0, 4.2)	1.1 (0.1, 4.0)	0.5 (0.1, 1.7)	0.7 (0.2, 1.7)	0.6 (0.2, 1.4)

Table 2.7.3.1-5: Important Identified Risk: Macrophage Activation Syndrome/Haemophagocytic Lymphohistiocytosis

Important Identified Risk: Macrophage Activation Syndrome/Haemophagocytic Lymphohistiocytosis

MAS/HLH from time of randomization	**Study BCM-003**	
	Liso-cel Arm	**SOC Arm**
Total number of subjects; n	92	91
Subjects with ≥ 1 AE; n	1	0
Grade 3 or 4; n (%)	0	0
Grade 5; n (%)	0	0
Subjects with ≥ 1 SAE; n (%)	0	0
Not Recovered/ Not Resolved; n (%)	0	0
Recovered/ Resolved; n (%)	0	0
Fatal; n (%)	0	0
Incidence (%) of subjects with ≥ 1 AE (95% CI)	1.1 (0.0, 5.9)	0 (0.0, 4.0)

Seriousness/Outcomes

In the 3L+ MCL Treated Set, no events of MAS/HLH events were reported.

In the Total Pooled 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Treated Set, serious MAS/HLH events were reported in 4 subjects. The MAS/HLH category included only the PT of Haemophagocytic lymphohistiocytosis.

Severity and Nature of Risk

Two Grade 5 MAS/HLH events were reported in the Total Pooled 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Treated Set, one in the 2L+ FL Treated Set and one in the Total LBCL Treated Set. No Grade 5 events were reported in the 3L+ MCL Treated Set.

Risk factors and risk groups	MAS/HLH is usually associated with severe or life-threatening (Grade 3 or 4) CRS and can be associated with viral, protozoal, bacterial, and fungal infections.[109]
Preventability	MAS/HLH should be suspected in patients who present with fever, liver function test abnormalities or liver failure, hepatosplenomegaly, cytopenia, very high ferritin levels,

Table 2.7.3.1-5: Important Identified Risk: Macrophage Activation Syndrome/Haemophagocytic Lymphohistiocytosis

Important Identified Risk: Macrophage Activation Syndrome/Haemophagocytic Lymphohistiocytosis	
	coagulopathy, and hypertriglyceridemia. There is not a definitive diagnostic test for MAS/HLH and the diagnosis is usually established by a clinical scoring system[110] and bone marrow biopsy evidence of erythrophagocytosis. Early diagnosis and treatment of MAS/HLH are important to prevent progression, organ failure and possibly death.
Impact on the risk-benefit balance of the product	MAS/HLH is a potentially life-threatening condition.
Public health impact	Serious MAS/HLH has been reported in up to 7% of patients treated with an approved anti-CD19 CAR T therapeutic. The morbidity and mortality associated with MAS/HLH is high, and early identification and supportive care are important to enable early and aggressive treatment with a combination of immunosuppression as well as treatment of immune triggers with broad spectrum antibacterial, antiviral, and antifungal therapy.[111] MAS is typically treated like high grade CRS with corticosteroids and tocilizumab, and additional anticytokine therapy with anakinra may be employed with careful management of intercurrent infection.
MedDRA terms	See Annex 7

Table 2.7.3.1-6: Important Identified Risk: Tumour Lysis Syndrome

Important Identified Risk: Tumour Lysis Syndrome	
Potential mechanisms	TLS is a consequence of cytokine release following on target pharmacology activity.
Evidence source and strength of evidence	In the 3L+ MCL Treated Set, 2.3% of subjects experienced TLS events. 1.1% of the events were severe and 1.1% of the events were fatal. TLS was reported in 4 of 826 subjects (0.5%) in the Total Pooled 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Treated Set. 0.4% of the events were severe and 0.1% of the events were fatal.
Characterization of risk	**Frequency with 95% CI** In the 3L+ MCL Treated Set, 2.3% of subjects experienced TLS events. 1.1% of the events were severe and 1.1% of the events were fatal. In the Total Pooled 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Treated Set 0.4% of subjects experienced severe TLS events. 0.5% of the events were ≥ Grade 3 with 0.1% of the events being fatal.

Table 2.7.3.1-6: Important Identified Risk: Tumour Lysis Syndrome

Important Identified Risk: Tumour Lysis Syndrome

TLS from time of infusion	3L+ MCL	2L+ FL	LBCL			Total 3L+ MCL,2L+ FL and 2L/3L+ LBCL
	017001 MCL Cohort	FOL-001	2L LBCL Total	3L+ LBCL Total	Total LBCL	Total Pooled
Total number of subjects; n	88	130	177	431	608	826
Subjects with ≥ 1 AE; n	2	0	0	2	2	4
Grade 3 or 4; n (%)	2 (2.3)	0	0	2 (0.5)	2 (0.3)	4 (0.5)
Grade 5; n (%)	1 (1.1)	0	0	0	0	1 (0.1)
Subjects with ≥ 1 SAE ; n (%)	1 (1.1)	0	0	0	0	1 (0.1)
Fatal; n (%)	1 (1.1)	0	0	0	0	1 (0.1)
Incidence (%) of subjects with ≥ 1 AE (95% CI)	2.3 (0.3, 8.0)	0 (0.0, 2.8)	0 (0.0, 2.1)	0.5 (0.1, 1.7)	0.3 (0.0, 1.2)	0.5 (0.1, 1.2)

Table 2.7.3.1-6: Important Identified Risk: Tumour Lysis Syndrome

Important Identified Risk: Tumour Lysis Syndrome

TLS from time of randomization	Study BCM-003	
	Liso-cel Arm	SOC Arm
Total number of subjects; n	92	91
Subjects with ≥ 1 AE; n	0	2
Grade 3 or 4; n (%)	0	1 (1.1)
Grade 5; n (%)	0	0
Subjects with ≥ 1 SAE; n (%)	0	0
Incidence (%) of subjects with ≥ 1 AE (95% CI)	0 (0.0, 3.9)	2.2 (0.3, 7.7)

Seriousness/Outcomes

In the 3L+ MCL Treated Set and in the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set, serious TLS events were reported in 1 subject with the reported outcome of fatal.

Severity and Nature of Risk

One fatal TLS event was reported in the 3L+ MCL Treated Set. No fatal TLS events were reported in the Total 2L+ FL and 2L/3L LBCL Sets. One fatal TLS event was reported in the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set.

Risk factors and risk groups	Based on the MOA for this risk, patients with high disease burden are at increased risk of developing TLS.
Preventability	Patients should be closely monitored for laboratory evidence of TLS (hyperuricemia, hyperkalaemia, hyperphosphatemia, and hypocalcaemia) and patients at high risk should receive prophylactic treatment as per standard clinical practice.
Impact on the risk-benefit balance of the product	TLS can cause life-threatening complications including death if not appropriately and immediately treated.
Public health impact	TLS is a significant complication of haematologic malignancies and their management. The syndrome consists of laboratory abnormalities either alone (laboratory TLS) or with clinical sequelae including renal failure, seizures, and arrhythmias (clinical TLS). Clinical TLS is a predictor for worse overall morbidity and mortality in cancer patients but can be prevented with administration of fluids, xanthine oxidase inhibitors and uricolytics. Patients at risk for TLS include those with high burden of disease by imaging, LDH or inflammatory markers.[112]

Table 2.7.3.1-6: Important Identified Risk: Tumour Lysis Syndrome

Important Identified Risk: Tumour Lysis Syndrome	
MedDRA terms	See Annex 7

Table 2.7.3.1-7: Important Identified Risk: Cytopenia, including Bone Marrow Failure

Important Identified Risk: Cytopenia, including Bone Marrow Failure	
Potential mechanisms	Cytopenia within the first month of liso-cel infusion result from pre-liso-cel LDC and targeted liso-cel B lymphocyte depletion, the latter consistent with the mechanism by which CD19 expressing B-cell malignancies are also depleted. Prolonged CAR T persistence and associated B-cell aplasia can also be associated with long-term cytopenia, consistent with the effect of other B-cell depleting agents such as rituximab.
Evidence source and strength of evidence	Prolonged cytopenia (laboratory values of haemoglobin, platelets or neutrophils ≥ Grade 3 at Day 35 for BCM-003 and Day 29 for Studies, 017001, 017006, 017007, BCM-001, FOL-001, and BCM-002) occurred in 35 subjects (39.8%) in the 3L+ MCL Treated Set, and 281 subjects (34.0%) in the Total 3L+ MCL, 2L+FL and 2L/3L+ LBCL Pooled Set. In the 3L+ MCL Treated Set, neutropenia (59.1%), anaemia (44.3%), and thrombocytopenia (29.5%) were the most commonly reported Grade ≥ 3 cytopenia TEAEs per PT in subjects. In the Total 3L+ MCL, 2L+FL and 2L/3L+ LBCL Pooled Set, the most frequent Grade ≥ 3 cytopenia AEs per PT were neutropenia occurring in 549 subjects (66.5%), followed by anemia in 366 subjects (44.3%), and thrombocytopenia occurring in 292 subjects (35.4%). In addition, Grade ≥ 3 cytopenia AEs of febrile neutropenia (7.7%), neutrophil count decreased (1.9%), platelet count decreased (0.7%), pancytopenia (0.5%), and bone marrow failure (0.4%) were reported.
Characterization of risk	**Frequency with 95% CI** Data for the frequency of prolonged cytopenia are presented below.

Prolonged Cytopenia from time of infusion	**3L+ MCL**	**2L+ FL**	**LBCL**			**Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL**
	017001 MCL Cohort	**FOL-001**	**2L LBCL Total**	**3L+ LBCL Total**	**Total LBCL**	**Total Pooled**
Total number of subjects; n	88	130	177	431	608	826
All AEs; n (%)	35 (39.8)	29 (22.3)	62 (35.0)	155 (36.0)	217 (35.7)	281 (34.0)

Table 2.7.3.1-7: Important Identified Risk: Cytopenia, including Bone Marrow Failure

Important Identified Risk: Cytopenia, including Bone Marrow Failure

Prolonged Cytopenia from time of randomization	**Study BCM-003**	
	Liso-cel Arm	**SOC Arm**
Total number of subjects; n	92	91
All AEs; n (%)	40 (43.5)	3 (3.3)

Data for the frequency of Cytopenia AEs are presented below.

Cytopenia AEs from time of infusion	**3L+ MCL**	**2L+ FL**	**LBCL**			**Total 3L+ MCL,2L+ FL and 2L/3L+ LBCL**
	017001 MCL Cohort	**FOL-001 (N=130)**	**2L LBCL Total (N=177)**	**3L+ LBCL Total (N=431)**	**Total LBCL (N=608)**	**Total Pooled (N=826)**
Subjects with ≥ 1 SAE; n						
Neutropenia	0	1	6	13	19	20
Anaemia	1	0	2	7	9	10
Thrombocytopenia	1	0	4	13	17	18
Febrile neutropenia	1	4	4	18	22	27
Neutrophil count decreased	NA	NA	NA	NA	NA	NA
Pancytopenia	0	0	0	1	1	1
Bone Marrow Failure	0	0	1	1	2	2
Platelet count decreased	NA	NA	NA	NA	NA	NA
Subjects with ≥ 1 AE; n						

Table 2.7.3.1-7: Important Identified Risk: Cytopenia, including Bone Marrow Failure

Important Identified Risk: Cytopenia, including Bone Marrow Failure						
Neutropenia	52	88	125	284	409	549
Anaemia	39	52	79	196	275	366
Thrombocytopenia	26	38	76	152	228	292
Febrile neutropenia	5	7	12	40	52	64
Neutrophil count decreased	0	6	10	0	10	16
Pancytopenia	0	0	0	4	4	4
Bone Marrow Failure	0	0	2	1	3	3
Platelet count decreased	0	3	3	0	3	6
Incidence (%) of subjects with ≥ 1 AE (95% CI)						
Neutropenia	59.1 (48.1, 69.5)	67.7 (58.9, 75.6)	70.6 (63.3, 77.2)	65.9 (61.2, 70.4)	67.3 (63.4, 71.0)	66.5 (63.1, 69.7)
Anaemia	44.3 (33.7, 55.3)	40.0 (31.5, 49.0)	44.6 (37.2, 52.3)	45.5 (40.7, 50.3)	45.2 (41.2, 49.3)	44.3 (40.9, 47.8)
Thrombocytopenia	29.5 (20.3, 40.2)	29.2 (21.6, 37.8)	42.9 (35.5, 50.6)	35.3 (30.8, 40.0)	37.5 (33.6, 41.5)	35.4 (32.1, 38.7)
Febrile neutropenia	5.7 (1.9, 12.8)	5.4 (2.2, 10.8)	6.8 (3.6, 11.5)	9.3 (6.7, 12.4)	8.6 (6.5, 11.1)	7.7 (6.0, 9.8)
Neutrophil count decreased	0 (0.0, 4.1)	4.6 (1.7, 9.8)	5.6 (2.7, 10.1)	0 (0.0, 0.9)	1.6 (0.8, 3.0)	1.9 (1.1, 3.1)
Pancytopenia	0 (0.0, 4.1)	0 (0.0, 2.8)	0.0 (0.0, 2.1)	0.9 (0.3, 2.4)	0.7 (0.2, 1.7)	0.5 (0.1, 1.2)
Bone Marrow Failure	0 (0.0, 4.1)	0 (0.0, 2.8)	1.1 (0.1, 4.0)	0.2 (0.0, 1.3)	0.5 (0.1, 1.4)	0.4 (0.1, 1.1)

Table 2.7.3.1-7: Important Identified Risk: Cytopenia, including Bone Marrow Failure

Important Identified Risk: Cytopenia, including Bone Marrow Failure

Platelet count decreased	0 (0.0, 4.1)	2.3 (0.5, 6.6)	1.7 (0.4, 4.9)	0.0 (0.0, 0.9)	0.5 (0.1, 1.4)	0.7 (0.3, 1.6)

Cytopenia AEs from time of randomization	**Study BCM-003**	
	SOC Arm (N=91)	**Liso-cel Arm (N=92)**
Subjects with ≥ 1 SAE; n		
Neutropenia	7	4
Anaemia	2	2
Thrombocytopenia	4	1
Febrile neutropenia	7	9
Neutrophil count decreased	NA	NA
Pancytopenia	0	0
Bone Marrow Failure	1	0
Platelet count decreased	NA	NA
Subjects with ≥ 1 AE; n		
Neutropenia	76	50
Anaemia	62	62
Thrombocytopenia	55	66
Febrile neutropenia	15	24
Neutrophil count decreased	NA	NA
Pancytopenia	0	0
Bone Marrow Failure	2	0
Platelet count decreased	NA	NA
Incidence (%) of subjects with ≥ 1 AE (95% CI)		
Neutropenia	82.6 (73.3, 89.7)	54.9 (44.2, 65.4)
Anaemia	67.4 (56.8, 76.8)	68.1 (57.5, 77.5)
Thrombocytopenia	59.8 (49.0, 69.9)	72.5 (62.2, 81.4)
Febrile neutropenia	16.3 (9.4, 25.5)	26.4 (17.7, 36.7)

Table 2.7.3.1-7: Important Identified Risk: Cytopenia, including Bone Marrow Failure

Important Identified Risk: Cytopenia, including Bone Marrow Failure

Neutrophil count decreased	NA	NA
Pancytopenia	0	0
Bone Marrow Failure	2.2 (0.3, 7.6)	0
Platelet count decreased	NA	NA

Seriousness/Outcomes

Serious events of neutropenia, febrile neutropenia, and anaemia were reported in the 3L+ MCL Treated Set. Serious events of neutropenia, anaemia, thrombocytopenia, febrile neutropenia, pancytopenia, and bone marrow failure were reported by subjects in the Total 3L+ MCL, 2L+FL and 2L/3L+ LBCL Pooled Set. The outcomes of these SAEs are summarised below.

Cytopenia SAEs from time of infusion	**3L+ MCL**	**2L+ FL**	**LBCL**			**Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL**
	017001 MCL Cohort	**FOL-001 (N=130)**	**2L LBCL Total (N=177)**	**3L+ LBCL Total (N=431)**	**Total LBCL (N=608)**	**Total Pooled (N=826)**
Not Recovered/ Not Resolved; n (%)						
Neutropenia	0	0	0	2 (0.5)	2 (0.3)	6 (0.7)
Anaemia	0	0	0	3 (0.7)	3 (0.5)	3 (0.4)
Thrombocytopenia	1 (1.1)	0	0	7 (1.6)	7 (1.2)	6 (0.7)
Febrile neutropenia	0	0	NA	NA	NA	0
Neutrophil count decreased	NA	NA	NA	NA	NA	NA
Pancytopenia	0	0	NA	NA	NA	0
Bone Marrow Failure	0	0	0	1 (0.2)	1 (0.2)	1 (0.1)

Table 2.7.3.1-7: Important Identified Risk: Cytopenia, including Bone Marrow Failure

Important Identified Risk: Cytopenia, including Bone Marrow Failure

Platelet count decreased	NA	NA	NA	NA	NA	NA
Recovered/ Resolved; n (%)						
Neutropenia	0	1 (0.8)	6 (3.4)	11 (2.6)	17 (2.8)	10 (1.2)
Anaemia	0	0	2 (1.1)	4 (0.9)	6 (1.0)	3 (0.4)
Thrombocytopenia	0	0	4 (2.3)	6 (1.4)	10 (1.6)	8 (1.0)
Febrile neutropenia	1 (1.1)	4 (3.1)	4 (2.3)	18 (4.2)	22 (3.6)	27 (3.3)
Neutrophil count decreased	NA	NA	NA	NA	NA	NA
Pancytopenia	0	0	0	1 (0.2)	1 (0.2)	1 (0.1)
Bone Marrow Failure	0	0	NA	NA	NA	0
Platelet count decreased	NA	NA	6 (3.4)	11 (2.6)	17 (2.8)	NA
Recovering/Resolving; n (%)						
Neutropenia	0	0	0	4 (0.9)	4 (0.7)	4 (0.5)
Anaemia	1 (1.1)	0	0	3 (0.7)	3 (0.5)	4 (0.5)
Thrombocytopenia	0	0	0	4 (0.9)	4 (0.7)	4 (0.5)
Bone Marrow Failure	0	0	1 (0.6)	0	1 (0.2)	1 (0.1)

Cytopenia SAEs from time of randomization	**Study BCM-003**	
	SOC Arm (N=91)	**Liso-cel Arm (N=92)**
Not Recovered/ Not Resolved; n (%)		
Neutropenia	0	4 (4.3)
Anaemia	0	1 (1.1)

Table 2.7.3.1-7: Important Identified Risk: Cytopenia, including Bone Marrow Failure

Important Identified Risk: Cytopenia, including Bone Marrow Failure

Thrombocytopenia	0	1 (1.1)
Febrile neutropenia	0	0
Neutrophil count decreased	NA	NA
Pancytopenia	0	0
Bone Marrow Failure	0	0
Platelet count decreased	NA	NA
Recovered/ Resolved; n (%)		
Neutropenia	4 (4.4)	3 (3.3)
Anaemia	2 (2.2)	1 (1.1)
Thrombocytopenia	1 (1.1)	3 (3.3)
Febrile neutropenia	9 (9.9)	7 (7.6)
Neutrophil count decreased	NA	NA
Pancytopenia	0	0
Bone Marrow Failure	NA	NA
Platelet count decreased	4 (4.4)	3 (3.3)
Recovering/Resolving; n (%)		
Bone Marrow Failure	0	1 (1.1)

Severity and Nature of Risk

No Grade 5 Cytopenia AEs were reported in the Total 3L+ MCL, 2L+FL and 2L/3L+ LBCL Pooled Set.

Cytopenia AEs from time of infusion	**3L+ MCL**	**2L+ FL**	**LBCL**			**Total 3L+ MCL and 2L+ FL and 2L/3L+ LBCL**
	017001 MCL Cohort	**FOL-001 (N=130)**	**2L LBCL Total (N=177)**	**3L+ LBCL Total (N=431)**	**Total LBCL (N=608)**	**Total Pooled (N=826)**
All AEs; n (%)						
Neutropenia	52 (59.1)	88 (67.7)	125 (70.6)	284 (65.9)	409 (67.3)	549 (66.5)

Table 2.7.3.1-7: Important Identified Risk: Cytopenia, including Bone Marrow Failure

Important Identified Risk: Cytopenia, including Bone Marrow Failure

Anaemia	39 (44.3)	52 (40.0)	79 (44.6)	196 (45.5)	275 (45.2)	366 (44.3)
Thrombocytopenia	26 (29.5)	38 (29.2)	76 (42.9)	152 (35.3)	228 (37.5)	292 (35.4)
Febrile neutropenia	5 (5.7)	7 (5.4)	12 (6.8)	40 (9.3)	52 (8.6)	64 (7.7)
Neutrophil count decreased	0	6 (4.6)	10 (5.6)	0 (0.0)	10 (1.6)	16 (1.9)
Pancytopenia	0	0	0 (0.0)	4 (0.9)	4 (0.7)	4 (0.5)
Bone Marrow Failure	0	0	2 (1.1)	1 (0.2)	3 (0.5)	3 (0.4)
Platelet count decreased	0	3 (2.3)	3 (1.7)	0 (0.0)	3 (0.5)	6 (0.7)
Grade 3 or 4 AEs; n (%)						
Neutropenia	49 (55.7)	79 (60.8)	121 (68.4)	267 (61.9)	388 (63.8)	516 (62.5)
Anaemia	33 (37.5)	13 (10.0)	54 (30.5)	149 (34.6)	203 (33.4)	249 (30.1)
Thrombocytopenia	22 (25.0)	15 (11.5)	58 (32.8)	119 (27.6)	177 (29.1)	214 (25.9)
Febrile neutropenia	4 (4.5)	7 (5.4)	8 (4.5)	38 (8.8)	46 (7.6)	57 (6.9)
Neutrophil count decreased	0	6 (4.6)	9 (5.1)	0	9 (1.5)	15 (1.8)
Pancytopenia	0	0	0	4 (0.9)	4 (0.7)	4 (0.5)
Bone Marrow Failure	0	0	2 (1.1)	1 (0.2)	3 (0.5)	3 (0.4)
Platelet count decreased	0	0	2 (1.1)	0	2 (0.3)	2 (0.2)

Table 2.7.3.1-7: Important Identified Risk: Cytopenia, including Bone Marrow Failure

Important Identified Risk: Cytopenia, including Bone Marrow Failure

Cytopenia AEs from time of randomization	**Study BCM-003**	
	SOC Arm (N=91)	**Liso-cel Arm (N=92)**
All AEs; n (%)		
Neutropenia	50 (54.9)	76 (82.6)
Anaemia	62 (68.1)	62 (67.4)
Thrombocytopenia	66 (72.5)	55 (59.8)
Febrile neutropenia	24 (26.4)	15 (16.3)
Neutrophil count decreased	NA	NA
Pancytopenia	0	0
Bone Marrow Failure	0	2 (2.2)
Platelet count decreased	NA	NA
Grade 3 or 4 AEs; n (%)		
Neutropenia	47 (51.6)	75 (81.5)
Anaemia	51 (56.0)	48 (52.2)
Thrombocytopenia	62 (68.1)	46 (50.0)
Febrile neutropenia	21 (23.1)	11 (12.0)
Neutrophil count decreased	NA	NA
Pancytopenia	0	0
Bone Marrow Failure	0	2 (2.2)
Platelet count decreased	NA	NA

Risk factors and risk groups	Previous anti-cancer therapy (chemotherapy, radiation) and LDC predispose to cytopenia.
Preventability	Complete blood counts should be monitored before and after liso-cel infusions and carefully followed, with transfusions and growth factor support provided in accordance with local practice standards.
Impact on the risk-benefit balance of the product	Prolonged cytopenia are an important aspect of liso-cel benefit risk and management, but the great majority of patients treated can be managed with conventional supportive care that is well established for patients treated with either stem cell transplant or cellular therapies.
Public health impact	The overall risk of cytopenia depends on the marrow lineage affected, the severity, duration and associated comorbidities that may predispose to infection or bleeding, and the responsiveness to therapy. Risk management activities utilised in the clinical trial setting (monitoring and replacement transfusions with red blood cells or platelets and colony stimulating factors) have been largely successful in managing this risk.

Table 2.7.3.1-7: Important Identified Risk: Cytopenia, including Bone Marrow Failure

Important Identified Risk: Cytopenia, including Bone Marrow Failure	
MedDRA terms	See Annex 7

Table 2.7.3.1-8: Important Identified Risk: Secondary Malignancy of T-cell Origin

Important Identified Risk: Secondary Malignancy of T-cell Origin	
Potential mechanisms	A theoretical mechanism for secondary malignancy of T-cell origin is insertional oncogenesis following the use of lentiviral vectors in the manufacture gene of modified CAR T-cell therapies. Potential mechanisms such as vector enhancer-mediated activation of down-stream gene expression, insertional gene inactivation, or gene activation by 3'end truncation, may disrupt gene expression due to vector integration within or near proto-oncogenic loci.[113]
Evidence source and strength of evidence	In the 3L+ MCL Treated Set, no subjects reported events of secondary malignancy of T-cell origin during the treatment-emergent period (any time from initiation of liso-cel administration through and including 90 days following the final infusion of liso-cel) or during the post treatment-emergent period (period which starts from 91 days post the infusion of liso-cel). In the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set, 1 of 826 subjects (0.1%) reported secondary malignancy of T-cell origin during the treatment-emergent period (discussed below for Study 017001 with 3L+ LBCL). Based on the PRAC recommendation adopted on 13-Jun-2024 that considered secondary malignancy of T-cell origin as a class effect, the Breyanzi safety specification was updated with the risk of secondary malignancy of T-cell origin as an important identified risk. At the time of PRAC's signal assessment report, 4 cases of secondary malignancy of T-cell origin after Breyanzi infusion were reviewed. Of the 3 cases reported in clinical studies (received from the studies FOL-001, 17004, and 017001), the events of secondary malignancy of T-cell origin coded to the PTs of Peripheral T-cell lymphoma (PTCL), TCL and Cutaneous TCL were reported in the subjects treated with Breyanzi infusion. The time to onset (TTO) in these 3 cases ranged from 30-434 days. The event outcome was reported as not recovered in 2 (from 017004 and 017001) subjects and fatal in 1 subject (from FOL-001) coded to the PT of TCL). One case of secondary malignancy of T-cell origin was received via post marketing registry. A patient developed the event of PTCL unspecified NOS 243 days after receiving Breyanzi infusion for the treatment of DLBCL, and subsequently died due to PTCL progression. Based on the tumour samples received and tested from the cases, no secondary malignancy due to insertional oncogenesis have been identified until the data cutoff dates.
Characterization of risk	**Frequency with 95% CI** In the 3L+ MCL Treated Set, no event of secondary malignancy of T-cell origin were reported. In the Total Pooled 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set, 1 subject (0.1%) reported secondary malignancy of T-cell origin (PT of peripheral T-cell lymphoma unspecified) during the treatment-emergent period. No subjects reported secondary malignancy of T-cell origin during the post treatment-emergent period. **Seriousness/Outcomes**

Table 2.7.3.1-8: Important Identified Risk: Secondary Malignancy of T-cell Origin

Important Identified Risk: Secondary Malignancy of T-cell Origin	
	In the 3L+ MCL Treated Set, no serious event of secondary malignancy of T-cell origin was reported. . A serious event of secondary malignancy of T-cell origin was reported in 1 subject (0.1%) in the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set. The outcome of this SAE was reported to be not recovered/not resolved. **Severity and Nature of Risk** In the 3L+ MCL Treated Set and in the Total 3L+ MCL,2L+ FL and 2L/3L+ LBCL Pooled Set, no Grade 5 events of secondary malignancy of T-cell origin were reported
Risk factors and risk groups	Patients with DLBCL have an increased risk of developing secondary malignancies - including T-cell neoplasms - related to prior chemo-, immuno-, and radiotherapy, and immunosuppression. Intrinsic risk factors that are common to both DLBCL and T-cell neoplasms include age, male gender, and lifestyle risk factors (eg, smoking). Much is unknown about the T-cell lymphomas after CAR T therapy that have been reported including important patient characteristics such as age, prior therapies (including prior autologous or allogeneic stem cell transplantation), immune status, and other clinical features as well as the time from CAR-T infusion to the development of T cell lymphoma.[114] The clinical status of the patients in terms of immunosuppression, previous therapy, conditioning chemotherapy, and evidence of prior clonal hematopoiesis is also unknown. Related to the product, the vector copy number, integration site analysis and detection of the CAR transgene in the T cell lymphomas are all crucial information for analysis. These data are critical to determine any possible biological or causal relationship with CAR T-cells but can be difficult to obtain as measurements of CAR expression or integration are not commercially available as clinical diagnostic assays.[114]
Preventability	Continuous long-term monitoring through Study GC-LTFU-001 and the postauthorisation observational registry-based Study BCM-005 enables further characterisation of this risk through reporting of secondary malignancies of T-cell origin, evaluation of secondary malignancies incidence by tumour histologic type and tumour liso-cel transgene testing as deemed appropriate.
Impact on the risk-benefit balance of the product	Secondary malignancy of T-cell origin is a serious and potentially fatal illness that will require medical intervention and is an important identified risk.
Public health impact	Whether T-cell neoplasms after CAR T-cell therapy occur more often than expected is an unanswered question because of the disease- and treatment-related risk factors and the rarity of T-cell neoplasms.[115] The estimated incidence proportion of T-cell lymphomas in patients commercially exposed to CD19- or BCMA-CAR T-cell therapies at the end of 2023 ranged from 0.04% to 0.06% in the CIBMTR population followed in post-authorization studies (median follow up time: 13 months) and in the total exposed population, respectively.[114]
MedDRA terms	See Annex 7

Table 2.7.3.1-9: Important Potential Risk: Autoimmune Disorders

Important Potential Risk: Autoimmune Disorders	
Potential mechanisms	Engagement by genetically-modified T-cells could theoretically promote a cytokine milieu with recruitment of other leukocytes to attack normal tissue, resulting in an acute or chronic inflammatory or autoimmune reaction. Recent analyses across CD19-targeted CAR T therapies suggest that only the minority of tumour-infiltrating T-cells are actually CAR T-cells but seem to be polyclonal immune cells that may have been activated by the CAR T-cells and the permissible cytokine milieu.[116] Hence, autoreactive T-cells could be activated by the CAR T-cells as bystander cells and could induce autoimmune phenomena. In addition, liso-cel cells retain their naïve T-cell receptor (TCR), which maintains physiological signalling activity. While the current understanding of CARs is that the CAR-derived supraphysiologic signal would override the physiologic TCR signal, the naïve TCR could be activated in the absence of CD19-antigen. If the target recognised by the naïve CAR was an autoantigen, activation could lead to autoimmune phenomena of the CAR-expressing T-cell.
Evidence source and strength of evidence	Until the cutoff dates, there have been no reports of subjects developing clinically evident autoimmune disorders after liso-cel therapy, nor has this been a prominent finding with CAR T-cell therapeutics in general.
Characterization of risk	**Frequency with 95% CI** In the 3L+ MCL Treated Set and in the Total 3L+ MCL, 2L+ FL and 2L /3L+ LBCL Pooled Set, no autoimmune disorders events were reported and this risk therefore remains theoretical. **Seriousness/Outcomes** In the 3L+ MCL Treated Set and in the Total 3L+ MCL, 2L+ FL and 2L /3L+ LBCL Pooled Set, no serious autoimmune disorders events were reported. **Severity and Nature of Risk** In the 3L+ MCL Treated Set and in the Total 3L+ MCL, 2L+ FL and 2L /3L+ LBCL Pooled Set, no autoimmune disorders events were reported.
Risk factors and risk groups	There have been no reports of new occurrence or exacerbation of an autoimmune disorder in liso-cel treated subjects. As such, risk groups or risk factors are unknown at this time.
Preventability	The testing for persistent vector sequences of RCL in the GC-LTFU-001 study in conjunction with long-term monitoring for delayed autoimmune AEs should help establish whether this potential risk remains only theoretical.
Impact on the risk-benefit balance of the product	The potential for autoimmune reactions is plausible with persistent transgene expression. The impact on the benefit/risk balance will depend on the frequency and severity of autoimmune AEs deemed causally related to prior liso-cel treatment.
Public health impact	Given that autoimmune disorders have not yet been reported to date in liso-cel treated subjects, the potential public health impact of this potential risk remains a matter of conjecture.
MedDRA terms	See Annex 7

Table 2.7.3.1-10: Important Potential Risk: Aggravation of Graft versus Host Disease

Important Potential Risk: Aggravation of Graft versus Host Disease	
Potential mechanisms	GvHD can occur after allo-HSCT when immune cells from the donor attack the recipient patient host's tissues. In patients after allo-HSCT, donor cells in the liso-cel product could theoretically induce aggravation of GvHD.
Evidence source and strength of evidence	There is a potential risk of inducing or aggravating GvHD in patients with prior allo-HSCT. Subjects with active acute or chronic GvHD were excluded from liso-cel clinical trials, and subjects had to be at least 3 months post allo-HSCT and clinically stable prior to apheresis. In the 3L+ MCL Treated Set and in the Total 3L+ MCL, 2L+ FL and 2L /3L+ LBCL Pooled Set, no subjects experienced an AE of aggravation of GvHD.
Characterization of risk	**Frequency with 95% CI** In the Total 3L+ MCL, 2L+ FL and 2L /3L+ LBCL Pooled Set, no subject experienced an AE of aggravation of GvHD during the treatment-emergent period. During the post-treatment-emergent period, in the Total LBCL Treated Set, a Grade 1 AE of GvHD of bowel and skin was reported on Study Day 228 in Study 017001 from a subject with 3L DLBCL transformed from indolent FL. The subject had undergone allo-HSCT more than 2 years prior to liso-cel infusion. The subject had a CR on Study Day 29 and the AE was reported as recovering/resolving with topical corticosteroids. The diagnosis of GvHD was not confirmed by biopsy. The subject had no reported history of GvHD prior to liso-cel therapy. **Seriousness/Outcomes** In the Total 3L+ MCL ,2L+ FL and 2L /3L+ LBCL Pooled Set, no serious event of GvHD were not reported. **Severity and Nature of Risk** In the Total 3L+ MCL, 2L+ FL and 2L /3L+ LBCL Pooled Set, no AEs of GvHD ≥ Grade 3 were reported in the post treatment-emergent period.
Risk factors and risk groups	Patients with active GvHD from prior HSCT.
Preventability	If there are no apparent treatment alternatives, the infusion of liso-cel should be delayed in patients with active GvHD pending a careful benefit/risk assessment performed by the treating prescriber. There is no experience in treating such patients to date and liso-cel is not recommended in this setting.
Impact on the risk-benefit balance of the product	The risk of GvHD in patients who have received allo-HSCT has not been determined. However, it is biologically plausible that the infusion and expansion of allogeneic CAR T-cells could aggravate GvHD.
Public health impact	Graft-versus-host disease is an adverse immunologic phenomenon observed in many patients after allo-HSCT. The incidence of GvHD is as high as 40% to 60% of patients receiving HSCT, depending on the type of transplant, patient characteristics, and GvHD prophylaxis regimen.[117] GvHD is a complex disease with acute and chronic presentations, multiorgan involvement, multispecialty management with many different treatment options and mortality may approach 15%.[118]
MedDRA terms	See Annex 7

Table 2.7.3.1-11: Important Potential Risk: Secondary Malignancies (except secondary malignancy of T-cell origin)

Important Potential Risk: Secondary Malignancies (except secondary malignancy of T-cell origin)	
Potential mechanisms	The risk of secondary malignancies (except secondary malignancies of T-cell origin) is confounded by factors related to the patient and previous lines of therapies as mentioned under Risk factors and risk groups. Some of the theoretical mechanisms linked to CAR T therapies, but not yet observed for liso-cel, include: • the transduction of cell types not of T-cell origin during manufacturing, which for liso-cel is minimized by a manufacturing process that is highly selective for T-cells, and controlled by the final drug product release specifications; • the in-vivo insertional mutagenesis associated with the generation of replication-competent lentivirus which is minimized by the liso-cel viral vector design which utilizes a 3rd-generation replication incompetent self-inactivating (SIN) design.
Evidence source and strength of evidence	In the 3L+ MCL Treated Set, 3 of 88 subjects (3.4%) reported secondary malignancies (except secondary malignancy of T-cell origin) during the treatment-emergent period (any time from initiation of liso-cel administration through and including 90 days following the final infusion of liso-cel). 14 of 82 subjects (17.1%) reported secondary malignancies (except secondary malignancy of T-cell origin) during the post treatment-emergent period (period which starts from 91 days post the infusion of liso-cel). 1 (1.2%) event was fatal. MCL survivors have an increased risk of secondary malignancies, particularly if treated with R-bendamustine. The intensive treatments needed for long-term remissions are a concern, and transition to treatment protocols with sustained efficacy but with a lower risk of secondary malignancies is needed.[119] In the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set, a total of 12 of 826 subjects (1.5%) reported secondary malignancies (except secondary malignancy of T-cell origin) during the treatment-emergent period (any time from initiation of liso-cel administration through and including 90 days following the final infusion of liso-cel). A total of 51 of 770 subjects (6.6%) reported secondary malignancies (except secondary malignancy of T-cell origin) during the post treatment-emergent period. 8 (1.0%) events were fatal. AEs that started after subsequent anticancer therapy or liso-cel retreatment are reported in the post treatment-emergent period, if subsequent anticancer therapy or retreatment started before 90 days post the final infusion of liso-cel.
Characterization of risk	**Frequency with 95% CI** In the 3L+ MCL Treated Set, 3.4% of subjects reported secondary malignancies (except secondary malignancy of T-cell origin) during the treatment-emergent period. During the post treatment-emergent period, 17.1% of subjects reported secondary malignancies (except secondary malignancy of T-cell origin). In the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set, 1.5% of subjects reported secondary malignancies (except secondary malignancy of T-cell origin) during the treatment-emergent period. 6.6% of subjects reported secondary malignancies (except secondary malignancy of T-cell origin) during the post treatment-emergent period.

Table 2.7.3.1-11: Important Potential Risk: Secondary Malignancies (except secondary malignancy of T-cell origin)

Important Potential Risk: Secondary Malignancies (except secondary malignancy of T-cell origin)

SPM (except secondary malignancy of T-cell origin) from time of infusion	**3L+ MCL**	**2L+ FL**	**LBCL**			**Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL**
	017001 MCL Cohort	**FOL -001**	**2L LBCL Total**	**3L+ LBCL Total**	**Total LBCL**	**Total Pooled**
Treatment-emergent period						
Total number of subjects; n	88	130	177	431	608	826
Subjects with ≥ 1 AE; n	3	2	1	6	7	12
Grade 3 or 4; n (%)	2 (2.3)	2 (1.5)	1 (0.6)	2 (0.5)	3 (0.5)	7 (0.8)
Grade 5; n (%)	0	0	0	0	0	0
Subjects with ≥ 1 SAE; n (%)	3 (3.4)	2 (1.5)	1 (0.6)	5 (1.2)	6 (1.0)	11 (1.3)
Not Recovered / Not Resolved; n (%)	2 (2.3)	2 (1.5)	0	2 (0.5)	2 (0.3)	6 (0.7)
Recovered / Resolved; n (%)	1 (1.1)	0	1 (0.6)	3 (0.7)	4 (0.7)	5 (0.6)
Fatal; n (%)	0	0	0	0	0	0
Incidence (%) of subjects with ≥ 1 AE (95% CI)	3.4 (0.7, 9.6)	1.5 (0.2, 5.4)	0.6 (0.0, 3.1)	1.4 (0.5, 3.0)	1.2 (0.5, 2.4)	1.5 (0.8, 2.5)
Post-treatment emergent period						

Table 2.7.3.1-11: Important Potential Risk: Secondary Malignancies (except secondary malignancy of T-cell origin)

Important Potential Risk: Secondary Malignancies (except secondary malignancy of T-cell origin)						
Total number of subjects; n	82	129	167	392	559	770
Subjects with ≥ 1 AE; n	14 (17.1)	8 (6.2)	5 (3.0)	24 (6.1)	29 (5.2)	51 (6.6)
Grade 3 or 4; n (%)	8 (9.8)	4 (3.1)	3 (1.8)	15 (3.8)	18 (3.2)	30 (3.9)
Grade 5; n (%)	1 (1.2)	2 (1.6)	1 (0.6)	4 (1.0)	5 (0.9)	8 (1.0)
Subjects with ≥ 1 SAE; n (%)	14 (17.1)	8 (6.2)	5 (3.0)	23 (5.9)	28 (5.0)	50 (6.5)
Not Recovered / Not Resolved; n (%)	5 (6.1)	4 (3.1)	3 (1.8)	8 (2.0)	11 (2.0)	20 (2.6)
Recovered /Resolved With Sequelae; n (%)	0	0	0	1 (0.3)	1 (0.2)	1 (0.1)
Recovered / Resolved; n (%)	8 (9.8)	2 (1.6)	1 (0.6)	10 (2.6)	11 (2.0)	21 (2.7)
Fatal; n (%)	1 (1.2)	2 (1.6)	1 (0.6)	4 (1.0)	5 (0.9)	8 (1.0)

Table 2.7.3.1-11: Important Potential Risk: Secondary Malignancies (except secondary malignancy of T-cell origin)

Important Potential Risk: Secondary Malignancies (except secondary malignancy of T-cell origin)

SPM (except secondary malignancy of T-cell origin) from time of randomization	**Study BCM-003**	
	Liso-cel Arm	**SOC Arm**
Treatment-emergent period		
Total number of subjects; n	92	91
Subjects with ≥ 1 AE; n (%)	1	1
Grade 3 or 4; n (%)	1 (1.1)	1 (1.1)
Grade 5; n (%)	1 (1.1)	0
Subjects with ≥ 1 SAE; n (%)	1 (1.1)	1 (1.1)
Not Recovered/ Not Resolved; n (%)	0	0
Recovered/ Resolved; n (%)	0	1 (1.1)
Fatal; n (%)	1 (1.1)	0
Incidence (%) of subjects with ≥ 1 AE (95% CI)	1.1 (0.0, 5.9)	1.1 (0.0, 6.0)
Post-treatment emergent period		
Total number of subjects; n	92	91
Subjects with ≥ 1 AE; n	2 (2.2)	2 (2.2)
Grade 3 or 4; n (%)	2 (2.2)	2 (2.2)
Grade 5; n (%)	0	0

Table 2.7.3.1-11: Important Potential Risk: Secondary Malignancies (except secondary malignancy of T-cell origin)

Important Potential Risk: Secondary Malignancies (except secondary malignancy of T-cell origin)		
Subjects with ≥ 1 SAE; n (%)	2 (2.2)	2 (2.2)
Not Recovered/ Not Resolved; n (%)	2 (2.2)	1 (1.1)
Recovered/ Resolved With Sequelae; n (%)	0	0
Recovered/ Resolved; n (%)	0	1 (1.1)
Fatal; n (%)	0	0

Seriousness/Outcomes

In the 3L+ MCL Treated Set, 3 subjects reported SAEs of secondary malignancies (except secondary malignancy of T-cell origin) during the treatment emergent period. During the post-treatment-emergent period, 14 subjects reported SAEs of secondary malignancies (except secondary malignancy of T-cell origin). 1 event was fatal.

In the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set, SAEs of secondary malignancies (except secondary malignancy of T-cell origin) were reported in 11 subjects during the treatment-emergent period. PTs reported included Acute myeloid leukemia, Adenocarcinoma of colon, Basal cell carcinoma, Colon cancer stage 0, Endometrial adenocarcinoma, Myelodysplastic syndrome, Squamous cell carcinoma of head and neck, and Squamous cell carcinoma of skin (1 subject each). During the post-treatment-emergent period, 50 subjects reported SAEs of secondary malignancies (except secondary malignancy of T-cell origin). 8 events were fatal.

Severity and Nature of Risk

No Grade 5 secondary malignancies (except secondary malignancy of T-cell origin) events were reported in the 3L+ MCL Treated Set during the treatment-emergent period. 1 Grade 5 event was reported in the post-treatment emergent period with reported PT squamous cell carcinoma of skin.

During the treatment-emergent period, no Grade 5 secondary malignancies (except secondary malignancy of T-cell origin) events were reported in the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set. During the post-treatment emergent period 8 Grade 5 secondary malignancies (except secondary malignancy of T-cell origin) events were reported. PTs reported included acute myeloid leukemia (4 subjects), myelodysplastic syndrome (2 subjects), squamous cell carcinoma of skin and lung adenocarcinoma (1 subject each).

Table 2.7.3.1-11: Important Potential Risk: Secondary Malignancies (except secondary malignancy of T-cell origin)

Important Potential Risk: Secondary Malignancies (except secondary malignancy of T-cell origin)	
Risk factors and risk groups	While none of the following may be exclusive, there may be several explanations why patients develop secondary malignancies: • Prior treatments for the B-cell lymphoma (eg, alkylating agents, immunomodulatory drugs, autologous HCT, and/or other therapies), • Patient's exposure to lymphodepleting chemotherapy prior to CAR T-cell infusion • Pre-existing mutations • Hereditary. Patients with LBCL, FL, and MCL have an increased risk of developing secondary malignancies related to prior chemotherapy, particularly for MDS and AML. Long-term persistence of CAR T-cells may be affected by the subsequent use of anti-EGFR mAbs, but no clinical data are currently available.
Preventability	Continuous long-term monitoring through Study GC-LTFU-001 and the postauthorisation observational registry-based study BCM-005 enables further characterisation of this risk through reporting of secondary malignancies and evaluation of secondary malignancies incidence by tumour histologic type.
Impact on the risk-benefit balance of the product	Secondary malignancies can be life-threatening (eg, metastatic ovarian carcinoma) or of lesser significance (eg, limited cutaneous basal cell carcinoma) depending on the tumour type and stage. The impact on product risk/benefit depends on the causal association with liso-cel therapy. To date there is insufficient evidence to suggest that liso-cel may play a causal role in any of the secondary malignancies observed in liso-cel clinical trials.
Public health impact	After surviving a primary malignancy, 17% to 19% of patients develop a secondary malignant neoplasm either as a random event, as a reflection of genetic susceptibility or as a result of mutation induced by prior genotoxic exposures, including prior mutagenic chemotherapy.[120]
MedDRA terms	See Annex 7

Table 2.7.3.1-12: Important Potential Risk: Generation of Replication Competent Lentivirus

Important Potential Risk: Generation of Replication Competent Lentivirus	
Potential mechanisms	RCL is a theoretical outcome of a lentivector genome recombination event resulting in the non-replicating vector acquiring the capacity to replicate.
Evidence source and strength of evidence	Lentiviral vectors used to transduce host autologous T-cells for liso-cel manufacture are engineered to be replication-incompetent and SIN. However, potential generation of RCL during manufacturing remains a theoretical possibility that cannot be entirely excluded and RCL has the potential to increase the possibility of liso-cel transgene mediated transformation and oncogenesis. In addition, there have been no reports of RCL generated during lentiviral vector manufacturing from liso-cel and there have been no liso-cel subjects who have developed RCL in vivo.
Characterization of risk	No case of RCL has been reported within the studies summarized in this RMP.

Table 2.7.3.1-12: Important Potential Risk: Generation of Replication Competent Lentivirus

Important Potential Risk: Generation of Replication Competent Lentivirus	
Risk factors and risk groups	No case of RCL has been reported within the studies summarized in this RMP.
Preventability	Modern vectors have been improved to reduce the risk of RCL generation. Liso-cel is manufactured using a third generation lentivector that is both SIN and non-replicating, and decreased homology between vector and packaging sequences has been shown to decrease the potential for virus formation. Replication competent lentivirus is tested in every lentiviral vector lot released, and all subjects treated in liso-cel clinical trials are scheduled to have peripheral blood evaluated for in vivo RCL, with none positive to date.
Impact on the risk-benefit balance of the product	The expected impact of RCL on the risk-benefit balance of liso-cel is potentially significant due to the risk of genotoxicity that may lead to secondary malignancies. Advances in lentivector engineering, however, make the likelihood of such an event highly unlikely.
Public health impact	The potential public health impact of this finding is considered low since no RCL have been observed in liso-cel human experience to date. RCL has not been detected in third-generation lentiviral products manufactured for clinical use suggesting that current vector design and vector product screening provide a high level of assurance regarding the absence of replicating virus.[121]
MedDRA terms	See Annex 7

Table 2.7.3.1-13: Important Potential Risk: Immunogenicity

Important Potential Risk: Immunogenicity	
Potential mechanisms	CAR T-cell immunotherapy has the potential to induce host immune responses. Immunogenicity induction risk factors have been shown to be associated with the presence of non-human or partially human sequences in the CAR construct, and also with the presence of residual viral proteins or other non-human origin proteins utilised as part of the gene editing step of CAR T production.[122]
Evidence source and strength of evidence	In the 2L+ FL Treated set, no subjects experienced AEs suggesting immunogenicity. In the Total Pooled 2L+ FL and 2L/3L+ LBCL Treated Set, 12.1% of subjects experienced AEs suggesting immunogenicity. 7.5% were mild and 4.2% of the events were moderate in severity. 0.4% of the events were severe with none being fatal. To be noted, AEs suggesting immunogenicity were reported in 19.8% of subjects in the SOC arm of Study BCM-003. Of those reported events, 1 (1.1%) event was ≥ Grade 3 and was life-threatening in severity. In the pooled studies (017001 and BCM-001, data cutoff date: 19-Jun-2020), pre-existing anti-therapeutic antibodies (ATAs) were detected in 29 (9%) of 309 subjects, and treatment-induced or treatment-boosted ATAs were detected in 46 (15%) of 304 subjects. The relationships between ATA status and efficacy, safety or PK were not conclusive due to the limited number of subjects with ATAs. In subjects who received one prior line of therapy for LBCL (BCM-003 [Arm B], 017006 and BCM-001 [Cohort 2]), pre-existing ATAs were detected in 0.6% (1/169) of subjects, and treatment-induced ATAs were detected in 7% (7/168) of subjects. Due to the low incidence of ATA, it is not appropriate to assess any potential relationship of ATA with efficacy, safety, or PK. Although there have been uncommon infusion related reactions after liso-cel therapy, there

Table 2.7.3.1-13: Important Potential Risk: Immunogenicity

Important Potential Risk: Immunogenicity

have not been reports characteristic of anaphylaxis, angioedema or urticaria as sometimes observed in association with immunogenic biologic therapies.

In the 3L+ FL group of study FOL-001, the prevalence of ATA was 1.9% (2 of 103 subjects); the incidence of ATA was 21.6% (22 of 102 subjects). One subject had treatment-boosted ATA. There were no clear differences in efficacy, safety, and PK between subjects who had treatment-induced or treatment-boosted ATA and subjects who did not have treatment-induced or treatment-boosted ATA. Similar results were observed in the 2L+ FL group.

In subjects who received liso-cel for 3L+ MCL, pre-existing ATAs were detected in 13% (11/88) of patients, and treatment-induced or treatment-boosted ATAs were detected in 20% (17/86) of patients. Due to the small number of subjects who had pre-existing, treatment-induced, or treatment-boosted ATA, the relationship between ATA status and efficacy, safety, or PK was not conclusive.

Characterization of risk

Frequency with 95% CI

In the 3L+ MCL Treated set, no subjects experienced AEs suggesting immunogenicity. In the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set, 10.8% of subjects experienced AEs suggesting immunogenicity.

Immunogenicity from time of infusion	**3L+ MCL**	**2L+ FL**	**LBCL**			**Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL**
	017001 MCL Cohort	**FOL-001**	**2L LBCL Total**	**3L+ LBCL Total**	**Total LBCL**	**Total Pooled**
Total number of subjects; n	88	130	177	431	608	826
Subjects with ≥ 1 AE; n	0	0	23	66	89	89
Grade 3 or 4; n (%)	0	0	1 (0.6)	2 (0.5)	3 (0.5)	3 (0.4)
Grade 5; n (%)	0	0	0	0	0	0
Subjects with ≥ 1 SAE; n (%)	0	0	0	0	0	0

Table 2.7.3.1-13: Important Potential Risk: Immunogenicity

Important Potential Risk: Immunogenicity

Incidence (%) of subjects with ≥ 1 AE (95% CI)	0 (0.0, 4.1)	0 (0.0, 2.8)	13.0 (8.4, 18.9)	15.3 (12.0, 19.1)	14.6 (11.9, 17.7)	10.8 (8.7, 13.1)

Immunogenicity from time of randomization	**Study BCM-003**	
	Liso-cel Arm	**SOC Arm**
Total number of subjects; n	92	91
Subjects with ≥ 1 AE; n	24	18
Grade 3 or 4; n (%)	3 (3.3)	1 (1.1)
Grade 5; n (%)	0	0
Subjects with ≥ 1 SAE; n (%)	1 (1.1)	1 (1.1)
Not Recovered/ Not Resolved; n (%)	0	0
Recovered/ Resolved; n (%)	1 (1.1)	1 (1.1)
Incidence (%) of subjects with ≥ 1 AE (95% CI)	26.1 (17.5, 36.3)	19.8 (12.2, 29.4)

Seriousness/Outcomes

In the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set, no serious AEs suggesting immunogenicity in association with liso-cel therapy have been reported.

Severity and Nature of Risk

Grade 3/4 events of immunogenicity have been reported for 3 subjects in the Total 3L+ MCL, 2L+ FL and 2L/3L+ LBCL Pooled Set. PTs reported included Rash maculo-papular (2 subjects) and Dermatitis exfoliative generalised (1 subject). No Grade 5 immunogenicity events have been reported.

Risk factors and risk groups	No known risk factors or risk groups.
Preventability	The use of LDC with fludarabine and cyclophosphamide (potent immunosuppressive agents) prior to liso-cel administration substantially reduces the potential for a clinically significant

Table 2.7.3.1-13: Important Potential Risk: Immunogenicity

Important Potential Risk: Immunogenicity	
	anti-liso-cel response. In addition, liso-cel targets CD19, a B-cell receptor, and liso-cel should therefore promote B-cell depletion, hypogammaglobulinaemia and reduced humoral responses. Finally, liso-cel is administered as a single IV infusion, which avoids the greater immunogenicity associated with subcutaneous or intradermal prime boost immunisation regimens.
Impact on the risk-benefit balance of the product	Pre-existing and post treatment ATA have not appeared with sufficient frequency to assess clinical impact, and therefore the impact on liso-cel risk-benefit remains unknown. The potential immunogenicity of liso-cel could potentially impact both efficacy and safety outcomes. To date there has been no clear correlation between immunogenicity, AEs and efficacy.
Public health impact	CAR T therapeutics can induce antibody and possibly cellular immune response to various components of the CAR neoantigen construct. Risk factors are primarily associated with the non-human or partially human nature of various components of the CAR T construct as well as the complexity of the CAR T production process requiring use of viral or other types of gene transfer procedures. In cases where immune responses have been observed, they were associated with a quick reduction in the CAR T count in vivo and a loss of efficacy. Strategies to reduce the theoretical immunogenicity risk of CAR T treatment include reduction of the viral protein content, humanisation of the CAR construct, LDC prior to CAR T-cell administration, and IV CAR T administration.[122] The potential public health impact of this potential risk is considered low based on what has been observed in liso-cel human experience to date: ATA have not been clearly associated with reductions in liso-cel cells in vivo.
MedDRA terms	See Annex 7

Table 2.7.3.1-14: Important Potential Risk: Transmission of Infectious Agents

Important Potential Risk: Transmission of Infectious Agents	
Potential mechanisms	Human and animal derived materials are used in the liso-cel manufacturing process (eg, human serum albumin and foetal bovine serum), and the manufacturing process includes open manipulations in a Grade A biosafety cabinet. Although testing of the materials for contaminants is performed prior to use in the manufacturing process and both personnel and facility controls are employed to maintain sterile conditions, it is not possible to completely eliminate the risk of cells becoming contaminated. However, incoming raw material controls, aseptic processing controls, and release testing for infectious agents (sterility, mycoplasma, etc.) reduce the possibility of transmission.
Evidence source and strength of evidence	A single subject has been reported as treated with liso-cel and later found to have a slow growing *Staphylococcus epidermidis* on the retained product. The subject did not have clinical evidence of infection but was cautiously treated for the potential of infection with antibiotics.
Characterization of risk	There have been no reports of transmission of infectious agents.
Risk factors and risk groups	Individuals in close contact with liso-cel including HCPs involved in the thawing, preparation and administration of liso-cel, and patients who are infused with liso-cel therapy.
Preventability	Stringent measures are in place to prevent the introduction of infectious agents to ensure liso-cel is manufactured in accordance with principles of Good Manufacturing Practices. Final

Table 2.7.3.1-14: Important Potential Risk: Transmission of Infectious Agents

Important Potential Risk: Transmission of Infectious Agents	
	release tests for infectious agents are conducted at the end of the manufacturing process to eliminate this possibility. Patients treated with liso-cel are frequently immunosuppressed and must be monitored for potential infections of bacterial, viral or fungal origin. Antibiotic prophylaxis should be considered for all patients about to receive lymphodepletion and liso-cel therapy in accordance with local practice guidelines.
Impact on the risk-benefit balance of the product	Infections resulting from any contaminated product have the potential to be serious or even fatal, and the managing physician should always be vigilant for infections caused by any organism in any organ system from any source.
Public health impact	The potential hazard of transmitting infectious pathogens through biologic products is a small but ever-present risk that is minimised by stringent liso-cel manufacturing processes and release criteria. To date there has been no public health impact of transmitted infections in the liso-cel clinical programme.
MedDRA terms	See Annex 7

Table 2.7.3.1-15: Important Potential Risk: Reduced Viability of Liso-cel due to Inappropriate Product Handling

Important Potential Risk: Reduced Viability of Liso-cel due to Inappropriate Product Handling	
Potential mechanisms	After release testing is complete, cryopreserved vials of liso-cel are shipped in a qualified temperature controlled shipper from the manufacturing facility in the [redacted] to a distribution depot in [redacted] where the product is temporarily stored prior to shipment to the infusion site after QP release. If any delays occur beyond the expiry of the shipper, the product is returned to the manufacturing facility and back up product vials are provided if available. Upon receipt at the infusion site, the product remains in the shipper (or liquid nitrogen storage) until the patient is ready to receive the infusion. When the product is removed from the shipper (or liquid nitrogen storage) it is thawed at room temperature and infused no more than two hours after removal from the shipper. Although clear instructions for storage and handling are provided with the product, it is not possible to completely eliminate the risk of inappropriate handling at the infusion site. If this does occur, the pharmacy/physician is instructed to inform the manufacturer to ensure altered product is not administered to the patient.
Evidence source and strength of evidence	There have been no reported cases of decreased liso-cel viability due to inappropriate product handling in the Pooled 3L+ MCL, 2L+ FL and 2L/3L+ LBCL studies.
Characterization of risk	There have been no reports of product mishandling to date.
Risk factors and risk groups	No known risk factors or risk groups.
Preventability	Liso-cel must be manufactured, distributed, measured and administered with precise specifications per the approved product prescribing information. As part of the RMP, HCPs involved in the handling of liso-cel will be provided with an educational tool with information on the safe thawing, preparation and appropriate administration of the product. As part of the RMP, HCPs involved in the handling of liso-cel will be

Table 2.7.3.1-15: Important Potential Risk: Reduced Viability of Liso-cel due to Inappropriate Product Handling

Important Potential Risk: Reduced Viability of Liso-cel due to Inappropriate Product Handling	
	provided with an educational tool with information on the safe thawing, preparation and appropriate administration of the product.
Impact on the risk-benefit balance of the product	There is potential risk of mishandling the product by clinical personnel involved in thawing, preparation and administration of liso-cel. To date, such incidence has not been reported. The product prescribing information and product handling information will clearly represent the necessary steps to minimise this potential risk.
Public health impact	No public health impact is anticipated, except for reduced benefit for individual patients with advanced malignancies who have been unresponsive to prior therapies and are seeking treatment benefit.
MedDRA terms	See Annex 7

2.7.3.2 Presentation of the Missing Information

Table 2.7.3.2-1: Missing Information

Missing Information	**Evidence Source**	**Population in need of further characterisation**
Impact on Pregnancy and Lactation	There is no information available from the clinical trial programme to determine the safety of liso-cel in pregnant or lactating patients. No cases of pregnancy or lactation have been reported in patients exposed to liso-cel.	Pregnant or lactating female patients exposed to liso-cel.
Long-term Safety	To date, there is limited information available from the clinical trial programme to determine long-term safety/delayed AEs for patients exposed to liso-cel. Persistent biological activity from gene modified (GM) T-cells could have adverse effects upon normal cell function, placing subjects at risk for development of AEs, some of which may be delayed by months or years. There are no AEs deemed related to prior liso-cel treatment reported through cutoff date for the liso-cel MAA filing from 26 3L+ DLBCL subjects treated for at least 2 years earlier, enrolled in liso-cel post exposure long-term follow-up study GC-LTFU-001.	All patients treated with liso-cel in clinical trials need to be followed for up to 15 years in the LTFU study starting from the date of the last infusion of GM T-cells, until study withdrawal, or death, whichever occurs first.
Safety in patients < 18 years old	There is insufficient information available to determine the safety of liso-cel in patients < 18 years old.	Subjects who are < 18 years of age, with CD19+ B-cell acute lymphoblastic leukaemia were being investigated in an clinical trial that has been terminated as the EMA has waived the obligation of a paediatric investigation plan for liso-cel in all paediatric populations based on the grounds that no significant benefit

Table 2.7.3.2-1: Missing Information

Missing Information	Evidence Source	Population in need of further characterisation
		can be expected over existing therapies. Subjects who accepted enrolment to study GC-LTFU-001 will be followed for up to 15 years.
Safety in Patients ≥ 75 years	Within the studies summarized in this RMP and their data cut dates, in the clinical study programme, 116 subjects aged ≥ 75 years have been treated (70 males and 46 females).	Subjects from ongoing trials and patients, followed longer-term, from the postauthorisation registry-based study BCM-005 aged ≥ 75 years of age.

2.8 Summary of the Safety Concerns

Safety concerns are summarized in Table 2.8-1.

Table 2.8-1: Summary of Safety Concerns

Important identified risks	Cytokine release syndrome
	Neurologic toxicity including ICANS
	Infections
	Hypogammaglobulinaemia
	Macrophage activation syndrome/haemophagocytic lymphohistiocytosis
	Tumour lysis syndrome
	Cytopenia, including bone marrow failure
	Secondary malignancy of T-cell origin
Important potential risks	Autoimmune disorders
	Aggravation of graft versus host disease
	Secondary malignancies (except secondary malignancy of T-cell origin)
	Generation of replication competent lentivirus
	Immunogenicity
	Transmission of infectious agents
	Reduced viability of liso-cel due to inappropriate product handling
Missing information	Impact on pregnancy and lactation
	Long-term safety
	Safety in patients < 18 years old
	Safety in patients ≥ 75 years

3 PART III: PHARMACOVIGILANCE PLAN

3.1 Routine Pharmacovigilance Activities

Bristol-Myers Squibb routine Pharmacovigilance activities are detailed in the Bristol-Myers Squibb Pharmacovigilance System Master File, and the Bristol-Myers Squibb Global Safety and Risk Management Standard Operating Procedures in accordance with "Good Pharmacovigilance Practices (GVP) in the EU."

In addition to expedited reporting, Bristol-Myers Squibb diligently undertakes follow-up on all ADRs, including serious ADRs that are provided to health authorities to ensure that sufficient case details are captured for optimal clinical evaluation. This includes efforts to obtain all relevant information and to establish the final outcome of the ADRs.

Emerging potential safety signals can be detected by both periodic and cumulative evaluation of ADRs. The results will be compiled in the PSUR in accordance with Guidelines on GVP in the EU/EEA.

In addition, data regarding identified and potential risks will be presented in the PSUR. The data presentation will include all case reports collected during the period covered by the PSUR together with cumulative data.

Using the data obtained from this plan, the benefit/risk profile of liso-cel will be re-evaluated on a periodic basis via the PSUR. If necessary, the related sections of the RMP will be updated accordingly.

3.1.1 Routine Pharmacovigilance Activities Beyond Adverse Reporting and Signal Detection

3.1.1.1 Specific Adverse Reaction Follow-up Questionnaires

Event specific questionnaires for the collection of AEs and follow-up data have been developed for the risks of secondary malignancies (including evaluation for insertional oncogenesis as applicable), CRS and NT including ICANS. The questionnaires have been developed to ensure that consistent and complete follow-up data are obtained. The forms are provided in Annex 4 of the RMP.

3.1.1.2 Other Forms of Routine Pharmacovigilance Activities

Not applicable.

3.2 Additional Pharmacovigilance Activities

3.2.1 Post-Authorisation Safety Study JCAR017-BCM-005

Liso-cel EU registry-based study (JCAR017-BCM-005) is a non-interventional PASS of patients treated with liso-cel therapy in its approved indications in the post-marketing setting (Annex 3). This observational study is being conducted based on secondary use of date from registries such as, but not limited to, the Center for International Blood and Marrow Transplant Research

(CIBMTR), and the European Group for Blood and Marrow Transplantation (EBMT) (Table 3.2.1-1). The registries are collecting data from patients until death or withdrawal of consent or up to 15 years, whichever occurs first.

Table 3.2.1-1: Post-Authorization Safety Studies Short Name Summary

Study short name and title	Rationale and study objectives	Study design	Study population	Milestone(s)
JCAR017-BCM-005 Non-interventional, post-authorization safety study (PASS) of patients treated with commercially available liso-cel (lisocabtagene maraleucel) for large B-cell lymphomas	Primary Objective: To characterise the incidence and severity of selected ADRs, as outlined in the SmPC, in patients treated with liso-cel in the post-marketing setting and to monitor for potential clinically important 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 post-marketing 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 not otherwise specified, high grade B-cell lymphoma [HGBCL]). • According to geographical regions (eg, Europe). • Subjects aged ≥ 75 years. • Subjects with comorbid conditions (eg, renal	Non-interventional PASS	Large B-cell lymphoma subtypes (eg, DLBCL, NOS, HGBCL, PMBCL, FL3B, FL) patients from existing independent registries, such as, but not limited to, the EBMT and CIBMTR	Protocol Submission to European Medicines Agency (EMA): 14-Apr-2022 Date of protocol approval by PRAC: 01-Dec-2022 Start of data collection[b]: collection[a] Q1 2023 Study Progress Updates: Per the PSUR cycle, according to the EURD list Interim reports[b]: At Year 5, 10, and 15 or when last patient is out of the registry-based study Date of Study Completion[c]: Q4 2042 Date of Final Study Report Submission to EMA: Q4 2043

Table 3.2.1-1: Post-Authorization Safety Studies Short Name Summary

Study short name and title	Rationale and study objectives	Study design	Study population	Milestone(s)
	impairment, reduced cardiac function). • Subjects with CNS involvement. • Subjects with ECOG performance score ≥ 2. • By possible prognostic factors (eg, high-risk IPI). • Subjects previously exposed to anti-CD19 therapy. • Subjects with low preleukapheresis absolute lymphocyte count (< 0.3 × 109/L). • Subjects treated with out-of-specification product.			

[a] 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 BCM-005 will take place 3 months after protocol approval from EMA.

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

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

3.2.2 US registry-based Study CA082-1175

Study CA082-1175 is designed to further evaluate the long-term safety profile of liso-cel therapy in patients treated in the United States for relapsed or refractory follicular lymphoma (R/R FL) who have received 2 or more prior lines of systemic therapy.

This is a non-interventional, single cohort, registry-based study which is based on secondary use of data obtained from the CIBMTR, an independent T-cellular therapy registry. Patients with R/R FL and treated with liso-cel therapy in the post-marketing setting will be eligible for this study. Patients will be followed from date of first liso-cel infusion for a maximum of 15 years (end of follow-up and of data extraction) or until death, loss to follow-up, or withdrawal of consent, whichever occurs first.

Table 3.2.2-1: US based Registry Study

Study short name and title	Rationale and study objectives	Study design	Study population	Milestone(s)
CA082-1175 Non-interventional cohort study of patients treated with liso-cel (lisocabtagene maraleucel) for relapsed/refractory follicular lymphoma in the postmarketing setting	Rationale: To support long-term postmarketing safety evaluation of liso-cel in the R/R FL indication. Primary Objectives: • To characterize the incidence and severity of selected AEs, including secondary malignancy, in patients receiving liso-cel to treat R/R FL. • To monitor for additional clinically important events that have not yet been identified as part of the liso-cel safety profile. Secondary Objective: • To assess the long-term effectiveness of liso-cel in patients with R/R FL.	Non-interventional, single cohort, registry-based study which is based on secondary use of data obtained from CIBMTR, an independenT-cellular therapy registry in the US.	Adult patients with R/R FL, who have received 2 or more prior lines of systemic therapy, who are treated in the postmarketing setting with at least 1 infusion of lisocel, are registered within the CIBMTR registry, have consented to share their data with MAHs, and fulfill all inclusion criteria and none of the exclusion criteria of this study	Start of data collection: 31-Aug-2024 corresponds to the date from which data extraction starts. Progress updates (eg, aligned with the reporting period of the PSURs); Interim reports: At Year 5 and 10 Date of Study Completion: End of Q1 2044 (Study completion 15 years after reaching the defined patient number, no further data will be included in the study analyses.) Date of Final Study Report Submission to EMA: Q4 2045

3.2.3 Long-term Follow-up Study

Study GC-LTFU-001 is an ongoing LTFU study of safety and efficacy for all paediatric and adult subjects exposed to a GM T-cell therapy in Bristol-Myers Squibb sponsored, or Bristol-Myers Squibb alliance partner sponsored, clinical trials in accordance with Health Authorities' guidance for long-term (up to 15 years) follow-up of subjects treated with gene therapy products (Table 3.2.3-1).

Table 3.2.3-1: Long-term Follow-up Study

Study short name and title	Rationale and study objectives	Study design	Study population	Milestone(s)
Long-term Follow-up Study (Study GC-LTFU-001)	Per Health Authority guidelines for gene therapy medicinal products that utilise integrating vectors (eg, retroviral vectors), 15 years of total long-term safety and efficacy follow-up of gene therapy treated subjects is required. The primary objectives of this study are: • To assess the risk of delayed AEs following exposure to gene modified (GM) T-cells. • To monitor for long-term persistence of GM T-cells, including analysis of vector integration sites, as appropriate. • To monitor for generation of replication competent lentiviruses (RCL). • To assess long-term efficacy following treatment with GM T-cells. • Describe growth—and sexual maturity status for subjects who were aged < 18 years at time of GM T-cell treatment. The secondary objective of this study is: • To monitor for B-cell levels in subjects who received CD19-directed GM T-cell therapy	Long-term follow-up of safety and efficacy for all paediatric and adult subjects exposed to a GM T-cell therapy in Bristol-Myers Squibb sponsored, or Bristol-Myers Squibb alliance partner-sponsored, clinical trials.	All paediatric and adult subjects exposed to a GM T-cell therapy in Bristol-Myers Squibb sponsored, or Bristol-Myers Squibb alliance partner-sponsored, clinical trials.	Subjects to be followed up for 15 years. Safety data will be reported in PSURs. Interim reports (5 and 10 years from FSFV [Jul-2018]): Q3 2023 and Q3 2028. LSLV: estimated Q3 2038. Final database lock: Q3 2038. Final report of completed GC-LTFU-001 follow-up of 3L+ large B-cell lymphoma liso-cel treated subjects: Q3 2039.

3.2.4 Transgene Assay Service Testing of Secondary Malignancies with Insertion Site Analysis as Applicable

Third-generation, self-inactivating (SIN) lentiviral vectors used in the manufacture of liso-cel. This modern vector system has significantly improved the safety profile with reduced risk of replication-competent lentiviruses (RCL) and insertional mutagenesis. The liso-cel drug product is highly purified for CD3+ cells, a population with an expected lower propensity for gene therapy-induced insertional mutagenesis based on both the natural history of wild-type HIV infection as well as on published long-term follow-up data from patients treated with CAR T-cells.[123] The transduction pool in the liso-cel manufacturing process has high T-cell purity so there is low risk of transducing nonT-cells.

With respect to LVV, the MAH intends to continue RCL release testing requirement of all manufactured LVV lots prior to their use in liso-cel drug product manufacturing process. [redacted] Notwithstanding, RCL testing will continue to be performed on patients post infusion as part of Study GC-LTFU-001 for liso-cel in the clinical settings. Up to the data cutoff dates, no RCL+ patients have been reported via Study GC-LTFU-001.

Additional pharmacovigilance activities will include the following, as detailed below:

- Specific CRF and specific adverse reaction follow-up templates are employed to characterise the clinical features and risk factors for secondary malignancies.
- For subjects who develop a new secondary malignancy, additional testing for vector sequence will be offered as described below in Sections 3.2.4.1 and 3.2.4.2. The MAH will include details of the methodology and the plans for additional testing for insertion site mapping if the testing for the presence of the vector sequence is detected.

The MAH proposes to present results of the transgene assay service in two ways. First, safety data will be included in DSURs and PSURs in accordance with EMA/816292/2011 Guideline on GVP. Second, presentation of results in reports will be submitted at 5, 10, and 15 years from the date of the European Commission Decision approving liso-cel.

3.2.4.1 Testing in the post-marketing setting

Transgene testing will be conducted for all reported secondary malignancies of suspected T-cell origin and other secondary malignancies where insertional oncogenesis is suspected, and a tumour sample is available. The MAH has developed a non-interventional laboratory testing protocol (protocol CA082-085), which is designed to test archived diagnostic tumor tissue samples from qualifying secondary malignancies in patients who received a BMS manufactured gene-modified product (including Breyanzi) and are not actively participating in a clinical trial.

When a secondary malignancy is reported, the specific adverse reaction follow-up questionnaire (Annex 4) will be employed to characterise all new malignancy reports and will collect the same information as from the structured secondary malignancy CRF used in Study GC-LTFU-001. A pathology review of the diagnosis will be conducted to ensure appropriate tissue with confirmed active disease is requested for transgene testing to mitigate risk of false negative results.

The MAH advises HCPs, via the national implemented educational programme, they should inform their patients about the importance of providing consent to transfer their samples for transgene testing. The MAH will encourage and assist prescribers in coordinating transfer of tumour and blood samples from patients with secondary malignancies for liso-cel transgene testing. The MAH will provide contact details for HCPs for tumour sample testing via the national implemented educational programme and in the product label. A sample of the tumour tissue with confirmed active disease involvement will be requested to test for the presence of liso-cel transgene. The most appropriate specimen for testing is the original diagnostic tumour sample previously collected and used for the diagnosis of the secondary malignancy. If the original diagnostic tumour sample is not available, a tumour sample collected after diagnosis and confirmed to have involvement with the secondary malignancy is acceptable. In the case of a secondary malignancy with bone marrow involvement, bone marrow aspirate is the preferred specimen over bone marrow biopsy for testing, if available. In addition to tumour samples, peripheral blood collected during the diagnosis of the secondary malignancy may also be requested for testing.

Tumor sample testing is a two-step process. The first test will utilize RNAscope in-situ hybridization (ISH) and/or droplet digital polymerase chain reaction (ddPCR), depending on the type of sample received for testing, to determine the presence of the applicable Gene Modified Cell Therapy (GMCT) transgene. If liso-cel transgene levels are detected at qualifying levels in the tumour specimen, insertion site analysis will be performed to assess the clonality of the transduced cell population by identifying the frequency and location of insertion sites to ascertain if insertional mutagenesis is suspected in the development of the malignancy. If insertional mutagenesis is suspected, additional optional exploratory testing to investigate the BMS GMCT drug product involvement in the development of the secondary malignancy may be conducted depending on availability of patient consent for testing and sample availability. Additional testing may include the assessment of DNA for germline/somatic mutation(s) and identification of the malignant clone(s), followed by assessment of RNA for transcriptome analysis to evaluate changes in gene expression potentially due to the transgene integration. If sufficient material remains, DNA may also be assessed for the presence of replication competent lentivirus. In the circumstance that limited sample is available, mutational analysis, TCR sequencing and whole transcriptome analysis will precede RCL testing.

Details for the types and amounts of tumour and blood samples acceptable for testing are shown in Table 3.2.4.1-1.

Table 3.2.4.1-1: Acceptable Sample Types and Corresponding Details for Transgene Testing

Sample Type[a]	Assay Allocation[b,c]
FFPE tumor sample	• [redacted] slides required for ISH • [redacted] slides allocated to ddPCR and/or ISA as applicable
Bone marrow aspirate	• DNA extraction for ddPCR and ISA if applicable

Table 3.2.4.1-1: Acceptable Sample Types and Corresponding Details for Transgene Testing

Sample Type[a]	Assay Allocation[b,c]
FFPE Bone marrow biopsy	• [redacted] slides required for ISH • [redacted] slides allocated to ddPCR and/or ISA as applicable
Peripheral blood	• DNA extraction for ddPCR and ISA if applicable

[a] Prior to acquiring a tumor sample, a pathology review of the diagnosis should be conducted to ensure appropriate tissue with confirmed active disease is requested for transgene testing to mitigate risk of false negative results.

[b] Residual tumor tissue or peripheral blood and/or DNA derived from the tumor or blood sample may be used for optional exploratory research if the sample qualifies for further testing and appropriate patient consent has been obtained.

[c] Sample types and quantities listed on this table may be modified depending on the event and sample availability.

3.2.4.2 Testing in Study GC-LTFU-001

Patients enrolled in Study GC-LTFU-001 will be followed for up to 15 years after the last infusion of liso-cel, or until study withdrawal, lost to follow-up or death, whichever occurs first. Testing for liso-cel transgene will be conducted on all secondary malignancies that require testing as per protocol where tissue is available. A structured secondary malignancy CRF is employed to characterise all new malignancy reports by dates of liso-cel treatment and new malignancy onset, time to onset, stage, history of prior malignancies, previous cancer therapies, prior radiotherapy, other relevant exposures, family history, and biopsy report. Treatments for the secondary malignancy and clinical outcomes will also be collected.

If a secondary malignancy is reported while a patient is enrolled on GC-LTFU-001 and is deemed to require transgene testing as per protocol, a sample of the neoplastic tissue used for the diagnosis of the secondary malignancy will be requested for testing. The neoplastic tissues submitted for testing will be evaluated for the presence of liso-cel transgene. If the transgene levels are detected at qualifying levels in the tumour specimen, insertion site analysis will be performed to assess the clonality of the CAR transduced cell population by identifying the frequency and location of vector integration sites to ascertain if insertional mutagenesis is suspected. If insertional mutagenesis is suspected, additional optional exploratory testing may be conducted as described in Section 3.2.4.1 to investigate the BMS GMCT drug product involvement in the development of the secondary malignancy. Testing may be conducted depending on availability of patient consent for testing and sample availability. The research may involve genetic tests using DNA or RNA; this may consist of the analysis of one or more candidate genes, analysis of genetic markers throughout the genome, or analysis of the entire genome. Testing may include, but is not limited to, TCR profiling by TCR sequencing, mutational analysis by whole genome sequencing, transcriptome analysis by RNA sequencing, and/or generation of replication competent lentiviruses. For prioritization of analysis with limited tissue materials, insertion site analysis, TCR sequencing and mutational analysis will

precede RCL testing. When a secondary malignancy is reported, blood samples will also be requested for quantification of liso-cel transgene and presence of RCL in peripheral blood

In addition to transgene testing for secondary malignancies, patients enrolled in Study GC-LTFU-001 are routinely monitored by safety assessments, clinical laboratory evaluations, as well as testing for persistence of vector sequence and RCL in peripheral blood at scheduled intervals as defined per protocol. [redacted] If clonal outgrowth is detected in the peripheral blood, patients will be closely monitored at more frequent intervals and for clinical abnormalities or development of a secondary malignancy.

3.3 Summary Table of Additional Pharmacovigilance Activities

Table 3.3-1: Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
PASS (JCAR017-BCM-005) / Ongoing	Primary Objective: To characterise the incidence and severity of selected ADRs, as outlined in the SmPC, in patients treated with liso-cel in the postmarketing setting, and to monitor for potential clinically important 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, DLBCL not otherwise specified, high grade B-cell lymphoma) [HGBCL], PMBCL, FL3B, and FL). • According to geographical regions (eg, Europe). • Subjects aged ≥ 75 years. • Subjects with comorbid conditions (eg, renal impairment, reduced cardiac function). • Subjects with secondary CNS involvement. • Subjects with ECOG performance score ≥ 2. • By possible prognostic factors (eg, high-risk IPI). • Subjects previously exposed to anti-CD19 therapy. • Subjects with low pre-leukapheresis absolute lymphocyte count (< 0.3×10^9/L). • Subjects treated with out-of-specification product.	CRS/MAS[a]/HLH[a] NT including ICANS[b] Infections Hypogammaglobulinaemia TLS Cytopenia, including bone marrow failure Secondary malignancy of T-cell origin Secondary malignancies (except secondary malignancy of T-cell origin) Impact on pregnancy and lactation (for pregnancy events) Long-term safety Aggravation of GvHD[a] Safety in patients ≥ 75 years	Protocol Submission to EMA Date of protocol approval by PRAC Start of data collection[c] Study progress updates Interim reports[d] Date of Study Completion[e] Date of Final Study Report Submission to EMA	14-Apr-2022 01-Dec-2022 Q1 2023 Per the PSUR cycle, according to the EURD list At Year 5, 10, and 15 or when last patient is out of the registry-based study Q4 2042 Q4 2043

Table 3.3-1: Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				
Category 3 - Required additional pharmacovigilance activities				
LTFU study (GC-LTFU-001)/ Ongoing	Long-term follow-up of safety and efficacy for all paediatric and adult subjects exposed do a GM T-cell therapy in Bristol-Myers Squibb sponsored, or Bristol-Myers Squibb alliance partner sponsored, clinical trials in accordance with Health Authorities' guidance for long-term (up to 15 years) follow-up of subjects treated with gene therapy products.	Infections Cytopenia, including bone marrow failure Autoimmune disorders Secondary malignancy of T-cell origin Secondary malignancies (except secondary malignancy of T-cell origin) Impact on pregnancy and lactation Long-term safety Safety in patients < 18 years old Generation of replication competent lentivirus	Subjects to be followed up for 15 years. Interim reports (5 and 10 years from FSFV [Jul 2018]). LSLV Final database lock Final report of GC-LTFU-001 follow-up of 3L+ large B-cell lymphoma liso-cel treated subjects Safety data will be reported in PSURs.	 Q3 2023 and Q3 2028 Estimated Q3 2038 Q3 2038 Q3 2039 Submitted in accordance with the EURD list
Non-interventional cohort study of patients treated with liso-cel (lisocabtagene maraleucel) for	To characterize the incidence and severity of selected AEs, including secondary malignancy, and to assess the long-term effectiveness in patients receiving liso-cel to treat R/R FL.	CRS/MAS[a]/HLH[a] NT including ICANS[b] Infections Hypogammaglobulinaemia	Start of data collection Progress updates	31-Aug-2024 corresponds to the date from which data extraction starts. Aligned with the reporting period of the PSURs

Table 3.3-1: Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
relapsed/refractory follicular lymphoma in the postmarketing setting (CA082-1175) / Ongoing		TLS	Interim reports	At Year 5 and 10
		Cytopenia, including bone marrow failure		
		Secondary malignancy of T-cell origin	Date of Study Completion	End of Q1 2044 (Study completion 15 years after reaching the defined patient number, no further data will be included in the study analyses.)
		Secondary malignancies (except secondary malignancy of T-cell origin)		
		Impact on pregnancy and lactation (for pregnancy events)	Date of Final Study Report Submission to EMA	Q4 2045
		Long-term safety		
		Aggravation of GvHD[a]		
		Safety in patients ≥ 75 years		
Transgene assay service testing of secondary malignancies with insertion site analysis as applicable	Tumour tissue sample testing from patients that develop a secondary malignancy	Secondary malignancy of T-cell origin	Safety data will be reported in PSURs.	Submitted in accordance with the EURD list.
		Secondary malignancies (except secondary malignancy of T-cell origin)[f]	European Commission decision + 5 years	Q2 2027
			European Commission decision + 10 years	Q2 2032
			European Commission decision + 15 years	Q2 2037

[a] Included under the category of Other AEs considered related to liso-cel treatment in Study BCM-005.

[b] NT is a primary endpoint in Study BCM-005, which comprises symptoms of NT, including cerebral oedema.

[c] Based on the European Commission decision and protocol approval timeline. 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 BCM-005 will take place 3 months after protocol approved by EMA.

[d] Interim reports will be prepared at year 5, 10, and 15 after EC decision date or when 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.

[f] Only reported secondary malignancies where insertional oncogenesis is suspected and a sample is available

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Post-authorisation efficacy studies imposed to liso-cel in accordance with Article 14 of Regulation (EC) No 1394/2007 are described in Table 4-1.

Table 4-1: Planned and Ongoing Post-authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study / Status	Summary of objectives	Efficacy concerns addressed[a]	Milestone(s)	Due Date(s)
Efficacy studies which are conditions of the marketing authorisation				
Study CA082-1105 (Batch analysis with clinical outcomes from JCAR017-BCM-005) / Ongoing	In order to further assess the consistency of product quality and clinical outcomes, the MAH shall submit batch analysis and corresponding clinical safety and effectiveness data from a minimum of 30 lots of Breyanzi finished product used to treat patients included in a non-interventional study based on secondary use of data from existing registries, according to an agreed protocol. Based on this data the MAH will also provide an evaluation on the need for a revision of the finished product specifications. Interim reports will be provided after approximately 15 lots.	Consistency of product quality and clinical outcomes	Protocol submission	24-Jun-2022
			Start of data collection[b]: (with JCAR017-BCM-005)	Q1 2023[c]
			Interim report submission	31-Dec-2025
			Date of Final Report Submission to EMA:	31-Dec-2026[d]

[a] Immunogenicity will be evaluated in these studies as the development of an immune response to liso-cel could diminish efficacy.

[b] Depending on the European Commission decision and protocol approval timeline.

[c] 6-month safety reports will be provided with the PSUR submission (PSUR single assessment [PSUSA]) as determined by the EURD list.

[d] Any significant out of trend results will be reported immediately.

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

5.1 Routine Risk Minimisation Measures

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
Important Identified Risks	
Cytokine release syndrome	**Routine risk communication:** Related information is found in Sections 4.2, 4.4 and 4.8 of the SmPC and Sections 2, 3, and 4 of the PL. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Sections 4.2 Posology and method of administration Advice regarding monitoring for signs/symptoms of CRS and availability of tocilizumab, or suitable alternative measures to treat CRS in the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue. Section 4.4 Special warnings and precautions for use Detailed guidance on the identification, grading, and management of CRS PL Section 2 What you need to know before you are given liso-cel and Section 4 Possible side effects Description of the signs of CRS, and guidance to tell doctor straight away if the patient gets any of these signs **Other routine risk minimisation measures beyond the Product Information:** Liso-cel is administered by a HCP. **Legal Status:** Liso-cel is restricted to a medical prescription.
Neurologic toxicity including ICANS	**Routine risk communication:** Related information is found in Sections 4.2, 4.4, 4.7 and 4.8 of the SmPC and Sections 2, 3, and 4 of the PL. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 Posology and method of administration Advice regarding monitoring for neurologic events Section 4.4 Special warnings and precautions for use

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
	Detailed guidance on the identification, grading, and management of NT. Guidance on treatment if cerebral oedema is suspected Section 4.7 Effects on ability to drive and use machines Advice to refrain from driving or operating heavy machines due to potential neurologic events PL Section 2 What you need to know before you are given liso-cel and Section 4 Possible side effects Description of the signs of NT, and guidance to tell doctor straight away if the patient gets any of these signs Advice on driving and on using machines **Other routine risk minimisation measures beyond the Product Information:** Liso-cel is administered by a HCP. **Legal Status:** Liso-cel is restricted to a medical prescription.
Infections	**Routine risk communication:** Related information is found in Sections 4.4 and 4.8 of the SmPC and Sections 2 and 4 of the PL. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 Special warnings and precautions for use Warning not to administer to patients with clinically significant active infection or inflammatory disorder. Guidance on the monitoring and management of infections. Guidance on the importance of prevention measures for COVID-19. PL Section 2 What you need to know before you are given liso-cel Test and checks before administration, and advice on signs of infection Section 4 Possible side effects Description of the signs of infection, and guidance to tell doctor straight away if the patient gets any of these signs **Other routine risk minimisation measures beyond the Product Information:** Liso-cel is administered by a HCP.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
	Legal Status: Liso-cel is restricted to a medical prescription.
Hypogammaglobulinaemia	**Routine risk communication:** Related information is found in Sections 4.4 and 4.8 of the SmPC and Section 4 of the PL. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** <u>SmPC</u> Section 4.4 Special warnings and precautions for use Advice on monitoring immunoglobulin levels after treatment **Other routine risk minimisation measures beyond the Product Information:** Liso-cel is administered by a HCP. **Legal Status:** Liso-cel is restricted to a medical prescription.
Macrophage activation syndrome/haemophagocytic lymphohistiocytosis	**Routine risk communication:** Related information is found in Sections 4.4 and 4.8 of the SmPC. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** <u>SmPC</u> Section 4.4 Special warnings and precautions for use Guidance on the evaluation and treatment of MAS/HLH **Other routine risk minimisation measures beyond the Product Information:** Liso-cel is administered by a HCP. **Legal Status:** Liso-cel is subject to a restricted medical prescription.
Tumour lysis syndrome	**Routine risk communication:** Related information is found in Section 4.8 of the SmPC and Section 4 of the PL. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Liso-cel is administered by a HCP.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
	Legal Status: Liso-cel is restricted to a medical prescription.
Cytopenia, including bone marrow failure	**Routine risk communication:** Related information is found in Sections 4.4 and 4.8 of the SmPC and Sections 2 and 4 of the PL. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 Special warnings and precautions for use Guidance on the monitoring and management of cytopenia PL Section 2 What you need to know before you are given liso-cel and Section 4 Possible side effects Description of the signs of low red blood cells or platelets, and guidance to tell doctor straight away if the patient gets any of these signs **Other routine risk minimisation measures beyond the Product Information:** Liso-cel is administered by a HCP. **Legal Status:** Liso-cel is restricted to a medical prescription.
Secondary malignancy of T-cell origin	**Routine risk communication:** Related information is found in Sections 4.4 and 4.8 of the SmPC and Sections 2 and 4 of the PL. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 Special warnings and precautions for use Guidance on the monitoring and instructions to be followed in the event of secondary malignancy of T-cell origin. PL Section 2 What you need to know before you are given liso-cel and Section 4 Possible side effects Description of the signs of secondary malignancy of T-cell origin and guidance to tell doctor if the patient gets any of these signs. **Other routine risk minimisation measures beyond the Product Information:** Liso-cel is administered by a HCP.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
	Legal Status: Liso-cel is subject to a restricted medical prescription.
Important Potential Risks	
Autoimmune disorders	None. The safety concern can be addressed by conducting active monitoring with routine pharmacovigilance and additional pharmacovigilance activity (Study GC-LTFU-001).
Aggravation of graft versus host disease	**Routine risk communication:** Related information is found in Section 4.4 of the SmPC and Section 2 of the PL. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 Special warnings and precautions for use Infusion is not recommended in patients with active acute or chronic GvHD PL Section 2 What you need to know before you are given liso-cel Advice to tell doctor if patient has had a stem cell transplant in the last 4 months **Other routine risk minimisation measures beyond the Product Information:** Liso-cel is administered by a HCP. **Legal Status:** Liso-cel is subject to a restricted medical prescription.
Secondary malignancies (except secondary malignancy of T-cell origin)	**Routine risk communication:** Related information is found in Section 4.4 of the SmPC. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 Special warnings and precautions for use Guidance on the monitoring secondary malignancies **Other routine risk minimisation measures beyond the Product Information:** Liso-cel is administered by a HCP. **Legal Status:** Liso-cel is subject to a restricted medical prescription.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
Generation of replication competent lentivirus	Routine risk minimisation activities are not deemed necessary. The safety concern can be addressed by conducting active monitoring with routine pharmacovigilance and additional pharmacovigilance activity (Study GC-LTFU-001).
Immunogenicity	**Routine risk communication:** Related information is found in Sections 4.2and 4.8 of the SmPC and Section 3 of the PL. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 Posology and method of administration The patient should be pre-medicated with paracetamol and diphenhydramine or another H1-antihistamine. PL Section 3 How liso-cel is given The patient should be pre-medicated with paracetamol and an antihistamine medicine. **Other routine risk minimisation measures beyond the Product Information:** Liso-cel is administered by a HCP. **Legal Status:** Liso-cel is subject to restricted medical prescription.
Transmission of infectious agents	**Routine risk communication:** Related information is found in Sections 4.2, 4.4 (Risk of transmission of infectious agents exists. Guidance on monitoring patients for signs and symptoms of infections), and 6.6 of the SmPC; Section 2 of the PL; and Section 10 of the Labelling (Special precautions for disposal of unused medicinal products or waste materials derived from such medicinal products, if appropriate). **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 Posology and method of administration Precautions to be taken before handling or administering the medicinal product Section 6.6 Special precautions for disposal and other handling PL Section 2 What you need to know before you are given liso-cel

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
	Advice to tell doctor if patient has a HBV, HCV or HIV infection **Other routine risk minimisation measures beyond the Product Information:** Liso-cel is administered by a HCP. **Legal Status:** Liso-cel is subject to a restricted medical prescription.
Reduced viability of liso-cel due to inappropriate product handling	**Routine risk communication:** Related information is found in Sections 4.2, 6.3, 6.4, 6.5, and 6.6 of the SmPC; Section 5 of the PL; and Section 9 of the Labelling (Special storage conditions). **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 Posology and method of administration Details on total time from removal from frozen storage to patient administration Section 6.3 Shelf life Instructions for storage of the medicinal product and maximum time for use after thawing Section 6.4 Special precautions for storage Instructions for storage of the medicinal product Section 6.6 Special precautions for disposal and other handling Instructions for storage, handling, administration and disposal of the medicinal product **Other routine risk minimisation measures beyond the Product Information:** Liso-cel is administered by a HCP. **Legal Status:** Liso-cel is subject to a restricted medical prescription.
Missing Information	
Impact on pregnancy and lactation	**Routine risk communication:** Related information is found in Section 4.6 of the SmPC and Section 2 of the PL. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
	Section 4.6 Fertility, pregnancy and lactation Pregnancy status for women of child-bearing potential should be verified prior to starting treatment. PL Section 2 What you need to know before you are given liso-cel Advice to talk to doctor in the case of pregnancy or breast-feeding. **Other routine risk minimisation measures beyond the Product Information:** Liso-cel is administered by a HCP. **Legal Status:** Liso-cel is subject to a restricted medical prescription.
Long-term safety	None. The safety concern can be addressed by conducting active monitoring with routine pharmacovigilance and additional pharmacovigilance activity (Study GC-LTFU-001; Study JCAR017-BCM-005).
Safety in patients < 18 years old	**Routine risk communication:** Related information is found in Section 4.2 of the SmPC and Section 2 of the PL. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Liso-cel is administered by a HCP. **Legal Status:** Liso-cel is subject to a restricted medical prescription.
Safety in patients ≥ 75 years	None. The safety concern can be addressed by conducting routine pharmacovigilance and additional pharmacovigilance activities (Study JCAR017-BCM-005).

5.2 Additional Risk Minimisation Measures

Additional risk minimisation measures are provided in Table 5.2-1. Details of additional risk minimisation activities are provided in Annex 6.

Table 5.2-1: Additional Risk Minimisation Measures

	Objectives: The MAH will ensure that hospitals and their associated centres that dispense liso-cel are qualified in accordance with the agreed controlled distribution programme by:

Table 5.2-1: Additional Risk Minimisation Measures

Controlled Distribution Programme	• ensuring immediate, on-site access to 1 dose of tocilizumab per patient prior to liso-cel infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensuring that suitable alternative measures to treat CRS instead of tocilizumab are available on site; • healthcare professionals (HCPs) involved in the treatment of a patient have completed the educational programme. **Rationale for the additional risk minimisation activity:** In order to minimise the risks associated with the treatment of liso-cel, hospitals and their associated centres who have HCPs that prescribe, dispense and administer liso-cel must complete the educational programme by being provided with information in accordance with the agreed controlled distribution HCP Educational Programme. **Target audience and planned distribution path:** The target audience is HCPs who will prescribe and/or dispense and/or administer liso-cel. **Plans to evaluate the effectiveness of the interventions and criteria for success:** PSUR as per EU guidance, GVP (E+R) Criteria for Success: Process indicator: Quantification of provision of product to only qualified sites and only if the HCPs involved in the treatment of a patient have received the educational programme.
Healthcare Professional Educational Programme	**Objectives:** All HCPs who are expected to prescribe, dispense and administer liso-cel shall be provided with an HCP guide, which will contain information about: • identification of CRS and serious neurological adverse reactions including ICANS; • management of CRS and serious neurological adverse reactions including ICANS; • adequate monitoring of CRS and serious neurological adverse reactions including ICANS; • provision of all relevant information to patients; • ensuring immediate, on-site access to 1 dose of tocilizumab per patient prior to liso-cel infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on site; • risk of secondary malignancy of T-cell origin • contact details for tumour sample testing after development of a secondary malignancy of T-cell origin; • provide information about the safety and efficacy long-term follow up study and the importance of contributing to such a study; • ensure that adverse reactions are adequately and appropriately reported; • ensure that detailed instructions about the thawing procedure are provided. **Rationale for the additional risk minimisation activity:** The HCP educational tool is designed to minimise the risk of CRS and Neurotoxicity including ICANS and provide information on the management of the risk and the necessary steps to prevent life-threatening or fatal CRS and/or Neurotoxicity including ICANS. This tool is also designed to increase awareness of the risk of secondary malignancy of T-cell origin. **Target audience and planned distribution path:** The target audience is HCPs who are expected to prescribe, dispense and administer liso-cel.

Table 5.2-1: Additional Risk Minimisation Measures

	Actions: • Distribution in a targeted manner of Educational Programme tools to HCPs expected to use the product within qualified centres. **Plans to evaluate the effectiveness of the interventions and criteria for success:** PSUR as per EU guidance, GVP (E+R) Method of assessment: • AE reports to be reviewed on an ongoing basis. AEs to be summarised at the time of the PSUR • Assessment through PASS (JCAR017-BCM-005). To monitor and estimate adherence to early intervention guide for CRS and Neurotoxicity including ICANS (ie, liso-cel use). Criteria for Success: Outcome indicator: No significant increase in frequency and severity of CRS and NTs in the postmarketing setting as presented in the SmPC.
Patient Educational Programme	**Objectives:** All patients who receive liso-cel shall be provided with a patient card, which will contain the following key messages: • the risks of CRS and serious neurologic adverse reactions associated with liso-cel; • the need to report the symptoms of suspected CRS and neurotoxicity including ICANS to their treating doctor immediately; • the need to remain in the proximity of the location where liso-cel was received for at least 2 weeks following liso-cel infusion; • the need to carry the patient card at all times; • a reminder to patients to show the patient card to all HCPs, including in conditions of emergency, and a message for HCPs that the patient has been treated with liso-cel; • fields to record contact details of the prescriber and batch number. **Rationale for the additional risk minimisation activity:** To educate patients on the risk of CRS and NT including ICANS and encourage patients to carry the patient card at all times to minimise the risk of CRS and NT including ICANS and provide education on the early symptoms of the risks and the necessary step to call or see the treating physician to prevent CRS and/or NT including ICANS from becoming life-threatening or resulting in death. **Target audience and planned distribution path:** The target audience is the patient who will receive liso-cel. Actions: • Distribution of patient card by HCP prescribing/dispensing and/or administering liso-cel depending on national healthcare system. **Plans to evaluate the effectiveness of the interventions and criteria for success:** PSUR as per EU guidance, GVP (E+R) Criteria for Success: Outcome indicator: No significant increase in frequency and severity of CRS and NTs in the postmarketing setting as presented in the SmPC.

5.3 Summary Table of Risk Minimisation Measures

A summary of risk minimisation measures is provided in Table 5.3-1.

Table 5.3-1: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Cytokine release syndrome	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.4, PL Sections 2 and 3 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR **Additional risk minimisation measures:** • Educational programme for HCPs and patients • Controlled Distribution Programme	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire **Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175)
Neurologic toxicity including ICANS	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4 and 4.7, PL Sections 2 and 3 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR **Additional risk minimisation measures:** • Educational programme for HCPs and patients • Controlled Distribution Programme	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire **Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175)
Infections	**Routine risk minimisation measures:** SmPC Section 4.4, PL Section 2 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175) LTFU study (GC-LTFU-001)
Hypogammaglobulinaemia	**Routine risk minimisation measures:** SmPC Section 4.4 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.

Table 5.3-1: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175)
Macrophage activation syndrome/haemophagocytic lymphohistiocytosis	**Routine risk minimisation measures:** SmPC Section 4.4 - warnings, advice and management discussed SmPC Section 4.8 - histiocytosis haematophagic listed as an ADR **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175), considered as part of the spectrum of CRS.
Tumour lysis syndrome	**Routine risk minimisation measures:** SmPC Section 4.8 and PL Section 4 - listed as an ADR **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175)
Cytopenia, including bone marrow failure	**Routine risk minimisation measures:** SmPC Section 4.4, PL Section 2 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175) LTFU study (GC-LTFU-001)
Secondary malignancy of T-cell origin	**Routine risk minimisation measures:** SmPC Section 4.4, PL Section 2 - warnings, advice and management	**Routine pharmacovigilance activities beyond adverse**

Table 5.3-1: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	SmPC Section 4.8, PL Section 4 - listed as an ADR	**reactions reporting and signal detection:** Targeted follow-up questionnaire
	Additional risk minimisation measures: Educational programme for HCPs	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) LTFU study (GC-LTFU-001) Transgene assay service testing of secondary malignancies with insertion site analysis as applicable
Important Potential Risks		
Autoimmune disorders	**Routine risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001)
Aggravation of GvHD	**Routine risk minimisation measures:** SmPC Section 4.4, PL Section 2 - warnings, advice and management	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** Included under the category of Other AEs considered related to liso-cel treatment in PASS (JCAR017-BCM-005) and US registry study (CA082-1175)
Secondary malignancies (except secondary malignancy of T-cell origin)	**Routine risk minimisation measures:** SmPC Section 4.4 - warnings, advice and management	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:**

Table 5.3-1: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		PASS (JCAR017-BCM-005) US registry study (CA082-1175) LTFU study (GC-LTFU-001)
Generation of replication competent lentivirus	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001).
Immunogenicity	**Routine risk minimisation measures:** SmPC Section 4.2 and PL Section 3 - premedication with paracetamol and diphenhydramine or another H1-antihistamine SmPC Section 4.8 - listed as an ADR **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Transmission of infectious agents	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4 (Risk of transmission of infectious agents exists. Guidance on monitoring patients for signs and symptoms of infections), and 6.6, PL Section 2 and Labelling Section 10 - handling instructions **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None
Reduced viability of liso-cel due to inappropriate product handling	**Routine risk minimisation measures:** SmPC Sections 4.2, 6.3, 6.4, 6.5 and 6.6, PL Section 5 and Labelling Section 9 - handling instructions **Additional risk minimisation measures:** • Educational programme for HCPs • Controlled Distribution Programme	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Missing Information		

Table 5.3-1: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Impact on pregnancy and lactation	**Routine risk minimisation measures:** SmPC Section 4.6, PL Section 2- warnings and advice	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) and US registry study (CA082-1175) for pregnancy events LTFU study (GC-LTFU-001).
Long-term safety	**Routine risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175) LTFU study (GC-LTFU-001)
Safety in patients < 18 years old	**Routine risk minimisation measures:** SmPC Section 4.2, PL Section 2 - warnings and advice	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001).
Safety in patients ≥ 75 years	**Routine risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175)

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for BREYANZI (lisocabtagene maraleucel)

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

The BREYANZI Summary of Product Characteristics (SmPC) and its package leaflet provide essential information to healthcare professionals (HCPs) and patients on how BREYANZI should be used.

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

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

I. The medicine and what it is used for

BREYANZI is authorised for the treatment of adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and follicular lymphoma grade 3B (FL3B) after two or more lines of systemic therapy. BREYANZI is authorized for the treatment of adult patients with DLBCL, high grade B cell lymphoma (HGBCL), PMBCL, and FL3B, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy. BREYANZI is authorized for the treatment of adult patients with R/R FL after two or more lines of systemic therapy and for the treatment of adult patients with R/R MCL after at least 2 lines of systemic therapy, including a BTKi (see SmPC for the full indications).

Further information about the evaluation of BREYANZI’s benefits can be found in BREYANZI’s EPAR, including in its plain-language summary, available on the European Medicines Agency website: https://www.ema.europa.eu/en/medicines/human/EPAR/breyanzi

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

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

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

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute routine risk minimisation measures.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

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

II.A List of important risks and missing information

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

Important identified and potential risks, together with missing information, are summarised below.

List of important risks and missing information

Important identified risks	Cytokine release syndrome (CRS)
	Neurologic toxicity (NT) including ICANS
	Infections
	Hypogammaglobulinaemia
	Macrophage activation syndrome/haemophagocytic lymphohistiocytosis (MAS/HLH)
	Tumour lysis syndrome (TLS)
	Cytopenia, including bone marrow failure
	Secondary malignancy of T-cell origin
Important potential risks	Autoimmune disorders
	Aggravation of graft versus host disease (GvHD)
	Secondary malignancies (except secondary malignancy of T-cell origin)
	Generation of replication competent lentivirus (RCL)

List of important risks and missing information

	Immunogenicity
	Transmission of infectious agents
	Reduced viability of BREYANZI due to inappropriate product handling
Missing information	Impact on pregnancy and lactation
	Long-term safety
	Safety in patients < 18 years old
	Safety in patients ≥ 75 years

II.B Summary of important risks

Important identified risks

Cytokine Release Syndrome (CRS)	
Evidence for linking the risk to the medicine	Cytokine release syndrome has been reported with all anti-CD19 directed CAR T therapeutics and is considered intrinsic to the therapeutic class. In the 2L+ FL Treated Set, 57.7% of subjects experienced CRS. 42.3% of the events were mild and 14.6% of the events were moderate in severity. 1 (0.8%) event was severe with none being life-threatening in severity. In the Pooled 2L+ FL and 2L/3L+ LBCL Total Pooled Treated Set, 44.6% of subjects experienced CRS. 28.9% of events were mild and 14.2% of the events were moderate in severity. 7 (0.9%) of the events were severe and 4 (0.5%) events were life-threatening in severity. Cytokine release syndrome is considered an important identified risk as it requires careful monitoring and prompt intervention to minimise the potential for life-threatening or even fatal outcomes. Further evaluation of CRS frequency, severity, and potential risk factors will be conducted in the postmarketing setting with an observational registry-based study BCM-005 including patients followed for up to 15 years as applicable.
Risk factors and risk groups	Disease burden is a risk factor for LBCL patients for the important identified risk of CRS. Analysis of AEs by Baseline Disease Characteristic showed that greater disease burden (ie, SPD ≥ 50 cm^2 by computed tomography [CT] scan or lactate dehydrogenase [LDH] ≥ 500 U/L), or baseline inflammatory state (ie, C-reactive protein [CRP] ≥ 20 mg/L) were associated with higher rates of all-grade CRS. Early onset of CRS usually predicts more severe manifestations. Patients with greater DLBCL disease burden (higher SPD and/or LDH) or who have elevated baseline levels of inflammatory marker (CRP), are more likely to develop CRS. Overall, in the Pooled 2L Treated Set and the Pooled 3L+ LBCL Treated Sets, CRS was more frequent in subjects with higher disease burden (SPD ≥ 50 cm^2) or with more aggressive disease (HGBCL or subjects who required bridging chemotherapy). Disease burden is a risk factor for FL patients for the important identified risks of CRS. The incidence of CRS was numerically higher in FL patients with SPD ≥ 50 cm^2 than SPD < 50 cm^2, although a small sample size for SPD ≥ 50 cm^2 subgroup (n=24) limits the interpretability of this difference.

Important identified risks

	Disease burden does not seem to be a risk factor for MCL patients for the important identified risk of CRS. In 3L+ MCL, the overall frequency and severity of CRS was generally similar also between subjects with pre-LDC SPD < 50 cm² (n=73) and those with pre-LDC SPD ≥ 50 cm² (n=7), but the small sample size of the second group limits the interpretability of the results.
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Sections 4.2 and 4.4, Package Leaflet (PL) Sections 2 and 3 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an adverse drug reaction (ADR) **Additional Risk Minimisation Activities:** • Educational programme for HCPs and patients • Controlled Distribution Programme
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Postauthorisation safety study (PASS) (JCAR017-BCM-005) US registry study (CA082-1175)
Neurologic Toxicity (NT) including ICANS	
Evidence for linking the risk to the medicine	Neurologic toxicity including ICANS is an important identified risk due to its seriousness and potential for associated disability, including death, if left untreated. In addition to CRS, NT is an expected AE associated with CAR T-cell therapy. The diagnosis is based on characteristic clinical signs and symptoms following CAR T infusion. Neurologic toxicities are primarily managed with supportive care for low grade toxicity, and corticosteroids for more severe NT. As investigators were trained in the recognition and management of NT, the BREYANZI clinical studies used the investigator's judgment to prospectively identify all treatment-emergent AEs (TEAEs) considered to be NT related to BREYANZI and termed this finding iiNT. The maximum iiNT grade was determined by the highest grade of any component TEAE considered part of iiNT. In the 2L+ FL Treated Set, 16.2% of subjects experienced iiNT. 11.5% were mild and 1.5% of the events were moderate in severity. 3.1% of the events were severe with none being life-threatening or fatal. In the Total Pooled 2L+ FL and 2L/3L+ LBCL Treated Set, 23.3% of subjects experienced iiNT. 9.1% were mild and 6.8% of the events were moderate in severity. 6.5% of the events were severe and 0.9% were life-threatening in severity with none being fatal. No subjects had Grade 5 iiNT but some BREYANZI treated subjects had ongoing iiNT at the time of death from other causes. In the 2L+ FL Treated Set, no subjects reported events of cerebral oedema. In the Total Pooled 2L+ FL and 2L/3L+ LBCL Treated Set, there is one reported case of cerebral oedema in the context of iiNT- a localised, unilateral, Grade 2 right temporal oedema reported in a subject who was later determined to have DLBCL involvement of the CNS. In the post-marketing setting, there have been reports of cerebral oedema in the context of neurotoxicity in patients infused with BREYANZI in whom an association between cerebral oedema and BREYANZI infusion could not be excluded. Serious and life-threatening

Important identified risks

	reports of cerebral oedema have been reported after treatment with other CAR T products and CAR T product candidates.
Risk factors and risk groups	Disease burden is a risk factor for LBCL patients for the important identified risk of NT. Analysis of AEs by Baseline Disease Characteristic showed that greater disease burden (ie, SPD ≥ 50 cm2 by CT scan or LDH ≥ 500 U/L), or baseline inflammatory state (ie, CRP ≥ 20 mg/L) were associated with higher rates of all grade iiNT-. Overall, in the Pooled 2L Treated Set and the Pooled 3L+ LBCL Treated Sets, iiNT was more frequent in subjects with higher disease burden (SPD ≥ 50 cm^2) or with more aggressive disease (HGBCL or subjects who required bridging chemotherapy). Pre-existing secondary CNS lymphoma extension of DLBCL to the CNS does not appear to be associated with a greater risk for cerebral oedema in the context of ICANS. Disease burden is not a risk factor for FL patients for the important identified risk of NT. In 3L+ FL, there was no numerical difference in any grade iiNT rate in subjects with SPD ≥ 50 cm^2 and in subjects with SPD < 50 cm^2 (17% incidence, each), the incidence and severity of iiNT was the same irrespective of disease burden. Analysis of AEs by baseline inflammatory state (ie, CRP ≥ 20 mg/L) showed no differences in the frequency or severity of iiNT (or any other TEAE). Disease burden does not seem to be a risk factor for MCL patients for the important identified risk of NT. In 3L+ MCL, the overall frequency and severity of iiNT was generally similar (< 20% difference) in subjects with LDH ≥ ULN (n=41) and those with LDH < ULN (n=47).
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Sections 4.2, 4.4 and 4.7, PL Sections 2 and 3 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR **Additional Risk Minimisation Activities:** • Educational programme for HCPs and patients • Controlled Distribution Programme
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175)

Important identified risks

Infections	
Evidence for linking the risk to the medicine	In addition to the known risk of infection from the LDC with fludarabine and cyclophosphamide, BREYANZI can cause depletion of B-cells and increase a patients' risk for developing high grade and serious infections. In the 2L+FL Treated Set, 5.4% of subjects experienced ≥ Grade 3 treatment-emergent infections. 5.4% were severe and no events were life-threatening in severity or fatal. In the Total Pooled 2L+FL and 2L/3L+ LBCL Treated Set, 10.8% of BREYANZI treated subjects had ≥ Grade 3 treatment-emergent infections. 8.1% were severe and 1.8% of the events were life-threatening in severity with 0.9% of the events being fatal.
Risk factors and risk groups	There was a numerically higher percentage of subjects with Grade ≥ 3 infection in those with Grade ≥ 3 neutropenia prior to LDC (23.5%) than in those who had Grade ≤ 2 neutropenia prior to LDC (11.5%) in Study 017001.
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Section 4.4, PL Section 2 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175) Long-term follow-up (LTFU) study (GC-LTFU-001)
Hypogammaglobulinaemia	
Evidence for linking the risk to the medicine	Hypogammaglobulinaemia is caused by B-cell aplasia. It is an on target anti-CD19 effect consistent with the BREYANZI mechanism of action (MOA), as well as a known risk from prior treatment with rituximab and other drugs that can promote lymphopenia, including LDC with fludarabine and cyclophosphamide. In the 2L+ FL Treated Set, TEAEs of hypogammaglobulinaemia were noted in 3.8% of subjects in the treatment-emergent period and in 2.3% of subjects in the post treatment-emergent period. Grade ≥ 3 hypogammaglobulinaemia was not reported in any subjects in the treatment-emergent period and was reported in 0.8% of subjects in the post treatment-emergent period. In the Total Pooled 2L+ FL and 2L/3L+ LBCL Treated Set, TEAEs of hypogammaglobulinaemia were noted in 9.5% of subjects in the treatment-emergent period and in 4.4% of subjects in the post treatment-emergent period. Grade ≥ 3 hypogammaglobulinaemia was reported in 0.1% of subjects in the treatment-emergent period and was reported in 0.1% of subjects in the post treatment-emergent period.
Risk factors and risk groups	Prior treatment with rituximab and other drugs that can promote lymphopenia.
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Section 4.4 – warnings, advice and management discussed

Important identified risks

	SmPC Section 4.8 and PL Section 4 – listed as an ADR **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175)
Macrophage Activation Syndrome/Haemophagocytic Lymphohistiocytosis (MAS/HLH)	
Evidence for linking the risk to the medicine	In the 2L+ FL Treated set, 0.8% of subjects experienced a MAS/HLH event. 0.8% of events were fatal. In the Total Pooled 2L+ FL and 2L/3L+ LBCL Treated Set, 0.7% of subjects experienced MAS/HLH events. 0.6% of events were moderate and 0.3% of the events were life-threatening in severity. 0.3% of the events were fatal. Macrophage activation syndrome/HLH has been reported in association with approved CD19-directed CAR T-cell therapies.
Risk factors and risk groups	MAS/HLH is usually associated with severe or life-threatening (Grade 3 or 4) CRS and can be associated with viral, protozoal, bacterial, and fungal infections.
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Section 4.4 – warnings, advice and management discussed SmPC Section 4.8 – histiocytosis haematophagic listed as an ADR **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) and US registry study (CA082-1175), considered as part of the spectrum of CRS.
Tumour Lysis Syndrome (TLS)	
Evidence for linking the risk to the medicine	In the 2L+ FL Treated Set, no subjects experienced TLS events. TLS was reported in 2 of 738 subjects (0.3%) in the Total Pooled 2L+ FL and 2L/3L+ LBCL Treated Set, both events of TLS had CTCAE severity Grade 3 and neither were assessed as serious.
Risk factors and risk groups	Based on the MOA for this risk, patients with high disease burden are at increased risk of developing TLS.
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Section 4.8 and PL Section 4 - listed as an ADR **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175)

Important identified risks

Cytopenia, Including Bone Marrow Failure	
Evidence for linking the risk to the medicine	Prolonged cytopenia (laboratory values of haemoglobin, platelets or neutrophils ≥ Grade 3 at Day 35 for BCM-003 and Day 29 for Studies, 017001, 017006, 017007, BCM-001, FOL-001, and BCM-002) occurred in 29 subjects (22.3%) in the 2L+FL Treated Set and 246 subjects (33.3%) in the Total Pooled 2L+FL and 2L/3L+ LBCL Treated Set. In the 2L+FL Treated Set, neutropenia (67.7%), anaemia (40.0%), and thrombocytopenia (29.0%) were the most commonly reported TEAEs in subjects. In the Total Pooled 2L+FL and 2L/3L+ LBCL Treated Set, the most frequent Grade ≥ 3 cytopenia AEs per PT were neutropenia occurring in 497 subjects (67.3%), followed by anaemia in 327 subjects (44.3%), and thrombocytopenia occurring in 266 subjects (36.0%). In addition, Grade ≥ 3 cytopenia AEs of febrile neutropenia (8.0%), neutrophil count decreased (2.2%), platelet count decreased (0.8%), pancytopenia (0.5%), and bone marrow failure (0.4%)were reported.
Risk factors and risk groups	Previous anti-cancer therapy (chemotherapy, radiation) and LDC predispose to cytopenia.
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Section 4.4 and PL Section 2 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175) LTFU study (GC-LTFU-001)
Secondary malignancy of T-cell origin	
Evidence for linking the risk to the medicine	Based on the PRAC recommendation adopted on 13-Jun-2024 that considered secondary malignancy of T-cell origin as a class effect, the Breyanzi safety specification was updated with the risk of secondary malignancy of T-cell origin as an important identified risk. At the time of PRAC's signal assessment report, 4 cases of secondary malignancy of T-cell origin after Breyanzi infusion were reviewed. Of the 3 cases reported in clinical studies (received from the studies FOL-001, 17004, and 017001), the events of secondary malignancy of T-cell origin coded to the PTs of Peripheral T-cell lymphoma (PTCL), TCL and Cutaneous TCL were reported in the subjects treated with Breyanzi infusion. One case of secondary malignancy of T-cell origin was received via post marketing registry. A patient developed the event of PTCL unspecified NOS 243 days after receiving Breyanzi infusion for the treatment of DLBCL, and subsequently died due to PTCL progression. Based on the tumour samples received and tested from the cases summarized in this RMP, no secondary malignancy due to insertional oncogenesis have been identified until the data cutoff dates.

Important identified risks

Risk factors and risk groups	Patients with DLBCL have an increased risk of developing secondary malignancies - including T-cell neoplasms - related to prior chemo-, immuno-, and radiotherapy, and immunosuppression. Intrinsic risk factors that are common to both DLBCL and T-cell neoplasms include age, male gender, and lifestyle risk factors (eg, smoking).
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Section 4.4, PL Section 2 - warnings, advice and management SmPC Section 4.8, PL Section 4 - listed as an ADR **Additional Risk Minimisation Activities:** Educational programme for HCPs
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) LTFU study (GC-LTFU-001) Transgene assay service testing of secondary malignancies with insertion site analysis as applicable

Important potential risks

Autoimmune Disorders	
Evidence for linking the risk to the medicine	To date there have been no reports of subjects developing clinically evident autoimmune disorders after BREYANZI therapy, nor has this been a prominent finding with CAR T-cell therapeutics in general.
Risk factors and risk groups	There have been no reports of new occurrence or exacerbation of an autoimmune disorder in BREYANZI treated subjects. As such, risk groups or risk factors are unknown at this time.
Risk minimisation measures	**Routine Risk Minimisation Activities:** None **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001)

Aggravation of Graft versus Host Disease (GvHD)	
Evidence for linking the risk to the medicine	There is a potential risk of inducing or aggravating GvHD in patients with prior allo-HSCT. Subjects with active acute or chronic GvHD were excluded from BREYANZI clinical trials, and subjects had to be at least 3 months post allo-HSCT and clinically stable prior to apheresis. In the 2L+ FL Treated Set and the Total Pooled 2L+ FL and 2L /3L+ LBCL Treated Set, no subjects experienced an AE of aggravation of GvHD.
Risk factors and risk groups	Patients with active GvHD from prior HSCT.
Risk minimisation measures	**Routine Risk Minimisation Activities:**

Important potential risks

	SmPC Section 4.4, PL Section 2 – warnings, advice and management **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Included under the category of Other AEs considered related to BREYANZI treatment in postauthorisation observational registry-based study (JCAR017-BCM-005) and US registry study (CA082-1175).
Secondary Malignancies (except secondary malignancy of T-cell origin)	
Evidence for linking the risk to the medicine	In the 2L+ FL Treated Set, 2 of 130 subjects (1.5%) reported secondary malignancies (except secondary malignancy of T-cell origin) during the treatment-emergent period (any time from initiation of BREYANZI administration through and including 90 days following the final infusion of liso-cel). 8 of 129 subjects (6.2%) reported secondary malignancies (except secondary malignancy of T-cell origin) during the post treatment-emergent period (period which starts from 91 days post the infusion of BREYANZI). 2 (1.6%) events were fatal. In the Total Pooled 2L+ FL and 2L/3L+ LBCL Treated Set, a total of 9 of 738 subjects (1.2%) reported secondary malignancies (except secondary malignancy of T-cell origin) during the treatment-emergent period (any time from initiation of BREYANZI administration through and including 90 days following the final infusion of BREYANZI). A total of 37 of 688 subjects (5.4%) reported secondary malignancies (except secondary malignancy of T-cell origin) during the post treatment-emergent period. 7 (1.0%) events were fatal. AEs that started after subsequent anticancer therapy or BREYANZI retreatment are reported in the post treatment-emergent period, if subsequent anticancer therapy or retreatment started before 90 days post the final infusion of BREYANZI. Based on the tumour samples received and tested from the studies summarized in this RMP, no secondary malignancies due to insertional oncogenesis have been identified until the data cutoff dates.
Risk factors and risk groups	While none of the following may be exclusive, there may be several explanations why patients develop secondary malignancies: • Prior treatments for the B-cell lymphoma (eg, alkylating agents, immunomodulatory drugs, autologous HCT, and/or other therapies), • Patient's exposure to lymphodepleting chemotherapy prior to CAR T-cell infusion • Pre-existing mutations • Hereditary. Patients with DLBCL have an increased risk of developing secondary malignancies related to prior chemotherapy, particularly for MDS and AML. Long-term persistence of CAR T-cells may be affected by the subsequent use of anti-epidermal growth factor receptor (EGFR) monoclonal antibodies, but no clinical data are currently available.
Risk minimisation measures	**Routine Risk Minimisation Activities:**

Important potential risks

	SmPC Section 4.4 - warnings, advice and management **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175) LTFU study (GC-LTFU-001) Transgene assay service testing of secondary malignancies with insertion site analysis as applicable
Generation of Replication Competent Lentivirus	
Evidence for linking the risk to the medicine	Lentiviral vectors used to transduce host autologous T-cells for BREYANZI manufacture are engineered to be replication-incompetent and self-inactivating. However, the potential generation of RCL during manufacturing remains a theoretical possibility that cannot be entirely excluded and RCL has the potential to increase the possibility of BREYANZI transgene mediated transformation and oncogenesis. In addition, there have been no reports of RCL generated during lentiviral vector manufacturing from BREYANZI and there have been no BREYANZI subjects who have developed RCL in vivo.
Risk factors and risk groups	No known risk factors or risk groups.
Risk minimisation measures	**Routine Risk Minimisation Activities:** None **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001)
Immunogenicity	
Evidence for linking the risk to the medicine	In the 2L+ FL Treated set, no subjects experienced AEs suggesting immunogenicity. In the Total Pooled 2L+ FL and 2L/3L+ LBCL Treated Set, 12.1% of subjects experienced AEs suggesting immunogenicity. 7.5% were mild and 4.2% of the events were moderate in severity. 0.4% of the events were severe with none being fatal. To be noted, AEs suggesting immunogenicity were reported in 19.8% of subjects in the SOC arm of Study BCM-003. Of those reported events, 1 (1.1%) event was ≥ Grade 3 and was life-threatening in severity. In the pooled studies (017001 and BCM-001, data cutoff date: 19-Jun-2020), pre-existing anti-therapeutic antibodies (ATAs) were detected in 29 (9%) of 309 subjects, and treatment-induced or treatment-boosted ATAs were detected in 46 (15%) of 304 subjects. The relationships between ATA status and efficacy, safety or PK were not conclusive due to the limited number of subjects with ATAs.

Important potential risks

	In subjects who received one prior line of therapy for LBCL (BCM-003 [Arm B], 017006 and BCM-001 [Cohort 2]), pre-existing ATAs were detected in 0.6% (1/169) of subjects, and treatment-induced ATAs were detected in 7% (7/168) of subjects. Due to the low incidence of ATA, it is not appropriate to assess any potential relationship of ATA with efficacy, safety, or PK. Although there have been uncommon infusion related reactions after BREYANZI therapy, there have not been reports characteristic of anaphylaxis, angioedema or urticaria as sometimes observed in association with immunogenic biologic therapies. In the 3L+ FL group of study FOL-001, the prevalence of ATA was 1.9% (2 of 103 subjects); the incidence of ATA was 21.6% (22 of 102 subjects). One subject had treatment-boosted ATA. There were no clear differences in efficacy, safety, and PK between subjects who had treatment-induced or treatment-boosted ATA and subjects who did not have treatment-induced or treatment-boosted ATA. Similar results were observed in the 2L+ FL group.
Risk factors and risk groups	No known risk factors or risk groups.
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Section 4.2 and PL Section 3 - premedication with paracetamol and diphenhydramine or another H1-antihistamine SmPC Section 4.8 - listed as an ADR **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Transmission of Infectious Agents	
Evidence for linking the risk to the medicine	A single subject has been reported as treated with BREYANZI and later found to have a slow growing *Staphylococcus epidermidis* on the retained product. The subject did not have clinical evidence of infection but was cautiously treated for the potential of infection with antibiotics.
Risk factors and risk groups	Individuals in close contact with BREYANZI including HCPs involved in the thawing, preparation and administration of BREYANZI and patients who are infused with BREYANZI therapy.
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Sections 4.2, 4.4 (Risk of transmission of infectious agents exists. Guidance on monitoring patients for signs and symptoms of infections), and 6.6, PL Section 2 and Labelling Section 10 - handling instructions **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Reduced Viability of BREYANZI due to Inappropriate Product Handling	

Important potential risks

Evidence for linking the risk to the medicine	There have been no reported cases of decreased BREYANZI viability due to inappropriate product handling in the Pooled 2L+ FL and 2L/3L+ studies.
Risk factors and risk groups	No known risk factors or risk groups.
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Sections 4.2, 6.3, 6.4, 6.5 and 6.6, PL Section 5 and Labelling Section 9 - handling instructions **Additional Risk Minimisation Activities:** • Educational programme for HCPs • Controlled Distribution Programme
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Missing information

Impact on Pregnancy and Lactation	
Risk minimisation measures	**Routine Risk Minimisation Measures:** SmPC Section 4.6, PL Section 2 - warnings and advice **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) and US registry study (CA082-1175) for pregnancy events. LTFU study (GC-LTFU-001)
Long-term Safety	
Risk minimisation measures	**Routine Risk Minimisation Measures:** None **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) LTFU study (GC-LTFU-001)
Safety in Patients < 18 years old	
Risk minimisation measures	**Routine Risk Minimisation Measures:** SmPC Section 4.2, PL Section 2 - warnings and advice **Additional Risk Minimisation Activities:** None

Missing information

Additional activities	pharmacovigilance	**Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001).
Safety in Patients ≥ 75 years		
Risk minimisation measures		**Routine Risk Minimisation Measures:** None **Additional Risk Minimisation Activities:** None
Additional activities	pharmacovigilance	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) US registry study (CA082-1175)

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Category 1 and 2 on-going and planned additional pharmacovigilance activities

Study short name and title	Rationale and study objectives
Postauthorisation safety study JCAR017-BCM-005	Primary objective: To characterise the incidence and severity of selected ADRs, as outlined in the SmPC, in patients treated with BREYANZI in the post-marketing setting, and to monitor for potential clinically important events that have not yet been identified as part of the BREYANZI safety profile. Secondary objectives: • To assess long-term effectiveness in patients treated with BREYANZI in the post-marketing setting. • To assess the BREYANZI safety and effectiveness profile in certain subgroups including but not limited to: – By large B-cell lymphoma subtypes (eg, DLBCL not otherwise specified, high grade B-cell lymphoma, , high grade B-cell lymphoma [HGBCL], primary mediastinal B-cell lymphoma [PMBCL], follicular lymphoma grade 3B [FL3B] and follicular lymphoma [FL]). – 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.

Category 1 and 2 on-going and planned additional pharmacovigilance activities

Study short name and title	Rationale and study objectives
	– 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 (< 0.3 × 109/L). Subjects treated with out-of-specification product.

Planned and ongoing post-authorisation efficacy studies

Study short name and title	Summary of objectives
Efficacy studies which are conditions of the marketing authorisation	
Study CA082-1105 (Batch analysis with clinical outcomes from JCAR017-BCM-005)	To assess the consistency of product quality and clinical outcomes
Efficacy studies which are Specific Obligations	
None	NA

II.C.2 Other studies in post-authorisation development plan

Category 3 ongoing and planned additional pharmacovigilance activities

Study short name and title	Rationale and study objectives
Long-term Follow-up Study (Study GC-LTFU-001)	Per Health Authority guidelines for gene therapy medicinal products that utilise integrating vectors (eg, retroviral vectors), 15 years of total long-term safety and efficacy follow-up of gene therapy treated subjects is required. Primary objectives: • To assess the risk of delayed AEs following exposure to gene modified (GM) T-cells. • To monitor for long-term persistence of GM T-cells, including analysis of vector integration sites, as appropriate. • To monitor for generation of replication competent retroviruses (RCR). • To assess long-term efficacy following treatment with GM T-cells. • Describe growth and sexual maturity status for subjects who were aged < 18 years at time of GM T-cell treatment. Secondary objective: • To assess long term HRQoL following treatment with GM T-cells.
Non-interventional cohort study (Study CA082-1175)	Primary Objectives: • To characterize the incidence and severity of selected AEs, including secondary malignancy, in patients receiving BREYANZI to treat R/R FL. • To monitor for additional clinically important events that have not yet been identified as part of the BREYANZI safety profile. Secondary Objective: To assess the long-term effectiveness of BREYANZI in patients with R/R FL.

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

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CRS Follow up form

Neurotoxicity follow up form

Second Malignancy follow up form

Additional Questions

Fax: 908-673-9115 Telephone: 1-800-640-7854 Contact info at: http://www.globalbmsmedinfo.com

ADVERSE EVENT REPORT QUESTIONNAIRE **Cytokine Release Syndrome (CRS)** **NOTE: INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED.**		
PATIENT DEMOGRAPHICS		
Patient's initials: _____ Gender: ☐ Male ☐ Female	Patient's date of birth (dd/Mmm/yyyy): _____/_____/_____ OR Patient's age: _____ years	Study Protocol ID (if applicable): _____

SUSPECT PRODUCTS: Please provide suspect product(s) information (those products which are suspected to be associated with one or more adverse events).			
	Suspect Product #1 (CAR T Cell Product)	**Suspect Product #2**	**Suspect Product #3**
Product name	☐ Lisocabtagene maraleucel (Breyanzi) ☐ Idecabtagene vicleucel (Abecma) ☐ Other: _____		
Dose and regimen			
Route of administration			
Indication			
Treatment start date (dd/Mmm/yyyy)			
Treatment stop date (dd/Mmm/yyyy)			
Treatment duration (if start/stop dates unknown)			
Lot/batch number(s)			
Expiration date(s)			

Additional Questions

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

Overall CRS Grade per Lee, et al (2014) - choose one based on most severe symptom		
☐	Grade 1	Temperature ≥ 38.5 °C/101.3 °F
☐	Grade 2	Oxygen requirement < 40% FiO_2 or Hypotension responsive to intravenous fluids or single low-dose vasopressor or Grade 2 organ toxicity
☐	Grade 3	Oxygen requirement ≥ 40% FiO_2 or Hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis
☐	Grade 4	Life-threatening hypotension or Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
☐	Grade 5	Death

Seriousness Criteria (check all that apply)	
☐ Death Date of death (dd/Mmm/yyyy): ____/____/____ Cause of death: _____ Was autopsy performed? ☐ Yes ☐ No If yes, please provide autopsy report if available.	☐ Required or ☐ Prolonged hospitalization Admission date (dd/Mmm/yyyy): ___/____/____ Discharge date (dd/Mmm/yyyy): ___/____/____
☐ Life-threatening	☐ Congenital anomaly/birth defect
☐ Persistent or significant disability/incapacity	☐ Medically important event
	☐ Non-serious

Additional Questions

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Causality Assessment
In your opinion, what is the causal relationship between CRS and the CAR T therapy? ☐ Related ☐ Not related **If not related, please provide the cause of the CRS.**
Were alternate causes for the signs and symptoms ruled out? ☐ Yes ☐ No **If yes, please describe how these were ruled out.**

CRS Treatment

Was tocilizumab administered? ☐ Yes ☐ No

Dose	Therapy Dates (dd/Mmm/yyyy)	Response

Were corticosteroids (CS) administered? ☐ Yes ☐ No

Name of CS	Route	Dose	Therapy Dates (dd/Mmm/yyyy)	Response

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

Name of Pressor	Dose	Therapy Dates (dd/Mmm/yyyy)	Response

Additional Questions

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Were any other treatments administered? ☐ Yes ☐ No

Name of Treatment	Route	Dose	Therapy Dates (dd/Mmm/yyyy)	Response

Relevant Medical History

If no relevant medical history, please indicate so here: ☐ No relevant medical history

Please list relevant medical history below, including any infection history or treatment for infection, and any history (including severity and previous treatment) of hepatic, renal, pulmonary, or cardiac disease or impairment.

Disease State	Start Date

Concomitant Medications

Please list concomitant medications below. If the list is too long, please attach a printout of the patient's medications.

Drug Name	Indication	Dose/Frequency	Start Date	Stop Date

Please provide any supplemental information on a separate page.

Signature of Person Completing Form:	
Name of Person Completing Form (Print):	**Date Completed (dd/Mmm/yyyy):**
E-mail Address:	**Phone Number:**

Additional Questions

Fax: 908-673-9115 Telephone: 1-800-640-7854 Contact info at: http://www.globalbmsmedinfo.com

Drug Safety Data Privacy Notice:

Your personal data will be processed by Bristol Myers Squibb Company ("BMS") located at P.O. Box 640, Palatine, IL 60078- 0640, 800-332-2056, United States, or by one of its worldwide affiliates, to the extent and for as long as necessary, for the purposes of the compliance with drug safety legal obligations and for storage purposes.

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Additional Questions

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ADVERSE EVENT REPORT QUESTIONNAIRE
Neurotoxicity (NT)

NOTE: INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED.

PART A:
PATIENT DEMOGRAPHICS

Patient's initials: _____ Gender: ☐ Male ☐ Female	Patient's date of birth (dd/Mmm/yyyy): _____/_____/_____ OR Patient's age: _____ years	Study Protocol ID (if applicable): _____

Patient's Relevant Medical History

If no relevant medical history, please indicate so here: ☐ No relevant medical history

Please list relevant medical history below, including any history of seizure disorder or other neurologic disorders, CNS involvement of cancer, and presence of implants or medical devices in the CNS.

Disease State	Start Date

Concomitant Medications

Please list concomitant medications below. If the list is too long, please attach a printout of the patient's medications.

Drug Name	Indication	Dose/ Frequency	Start Date	Stop Date

--- See next page ---

Additional Questions

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PART B: SUSPECT PRODUCTS			
Suspect CAR T Cell Product	**Infusion date (dd/Mmm/yyyy)**	**Indication**	**Batch/JOIN number**
☐ Lisocabtagene maraleucel (Breyanzi) ☐ Idecabtagene vicleucel (Abecma) ☐ Other: _____			

OTHER SUSPECT PRODUCTS: Please provide suspect product(s) information (those products which are suspected to be associated with one or more adverse events).		
	Suspect Product #1	**Suspect Product #2**
Product name		
Dose and regimen		
Route of administration		
Indication		
Treatment start date (dd/Mmm/yyyy)		
Treatment stop date (dd/Mmm/yyyy)		
Treatment duration (if start/stop dates unknown)		
Expiration date(s)		
Batch/LOT number		

--- See next page ---

PART C:
NEUROLOGIC ADVERSE EVENTS

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Please complete the following details if the patient expierienced ICANS

	Start Date (dd/Mmm/yyyy)	Stop Date (dd/Mmm/yyyy)	Grading assessment[b]	Seriousness Criteria[b]	Outcome[c]	Causality[d]
ICANS						

Please describe the ICANS Sign and Symptoms

ICANS sign or symptom	Start Date (dd/Mmm/yyyy)	Stop Date (dd/Mmm/yyyy)	Grading assessment[b]	Seriousness Criteria[b]	Outcome[c]

Non-ICANS Neurologic Adverse Events

Please enter details regarding non-ICANS Neurologic Adverse Event(s) below, if any.

Non-ICANS Neurologic Adverse Event	Start Date (dd/Mmm/yyyy)	Stop Date (dd/Mmm/yyyy)	Grading assessment[b]	Seriousness Criteria[b]	Outcome[c]	Causality[d]

Key

[a]Grading assessment:
1 = Grade 1
2 = Grade 2
3 = Grade 3
4 = Grade 4
5 = Grade 5

[b]Seriousness Criteria
D = Death
LT = Life-threatening
H = Initial or prolonged hospitalization
S = Significant disability or incapacity
M = Medically significant
N/A = Not applicable (non-serious)

[c]Outcome
1 = Recovered/resolved
2 = Recovering/resolving
3 = Not recovered/not resolved
4 = Recovered/resolved with sequelae
5 = Fatal
6 = Unknown

[d]Causality
1= Related
2= Not related

CEREBRAL EDEMA

Was any cerebral edema identified? ☐ Yes ☐ No

Did the patient experience cerebral edema in the context of ICANS ? ☐ Yes ☐ No

Please describe

- **how it was identified.**

- **the cerebral edema treatment.**

If one of the neurologic adverse events resulted in death, please provide the following information.

Date of death (dd/Mmm/yyyy): _____/_____/_____

Cause of death: _____

Was an autopsy performed? ☐ Yes ☐ No If yes, please provide the autopsy report if available.

If one of the neurologic adverse events resulted in hospitalization, please provide the following information.

Admission date (dd/Mmm/yyyy): _____/_____/_____

Discharge date (dd/Mmm/yyyy): _____/_____/_____

DIAGNOSTIC RESULTS

Please add as many lines as needed.

Test name [e.g. spinal fluid results, brain imagin, other]	**Date of Test (dd/Mmm/yyyy)**	**Findings**

Additional Event Information

In your opinion, what is the causal relationship between the neurologic adverse events and the BMS CAR T therapy?

☐ Related ☐ Not related

If not related, what was the cause of the the neurologic adverse events?

Were alternative causes for the signs and symptoms ruled out? ☐ Yes ☐ No

If yes, please describe how these alternate causes were ruled out.

Neurologic adverse events treatment

Was tocilizumab administered? ☐ Yes ☐ No

Dose	Therapy Dates	Response

Were anti-epileptics administered? ☐ Yes ☐ No

Name of Anti-Epileptic	Route	Dose	Therapy Dates	Response

Were corticosteroids (CS) administered? ☐ Yes ☐ No

Name of CS	Route	Dose	Therapy Dates	Response

Were any other treatments administered? ☐ Yes ☐ No

Name of Treatment	Route	Dose	Therapy Dates	Response

Please provide any supplemental information on a separate page.

Additional Questions

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Signature of Person Completing Form:	
Name of Person Completing Form (Print):	**Date Completed (dd/Mmm/yyyy):**
E-mail Address:	**Phone Number:**

Additional Questions

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ADVERSE EVENT REPORT QUESTIONNAIRE **Secondary Malignancy** **NOTE: INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED.**		
PATIENT DEMOGRAPHICS		
Patient's initials: _____ Gender: ☐ Male ☐ Female	Patient's date of birth (dd/Mmm/yyyy): _____/_____/_____ OR Patient's age: _____ years	Study Protocol ID (if applicable): _____

SUSPECT PRODUCTS: Please provide suspect product(s) information (those products which are suspected to be associated with one or more adverse events).			
	Suspect Product #1 (CAR T Cell Product)	**Suspect Product #2**	**Suspect Product #3**
Product name	☐ Lisocabtagene maraleucel (Breyanzi) ☐ Idecabtagene vicleucel (Abecma) ☐ Other: _____		
Dose and regimen			
Route of administration			
Indication			
Treatment start date (dd/Mmm/yyyy)			
Treatment stop date (dd/Mmm/yyyy)			
Treatment duration (if start/stop dates unknown)			
Lot/batch number(s)			
Expiration date(s)			

SECONDARY MALIGNANCY					
If not previously reported, please provide the information below regarding the secondary malignancy.					
Secondary Malignancy	**Start Date (dd/Mmm/yyyy)**	**Stop Date (dd/Mmm/yyyy)**	**CTCAE Grade[a]**	**Seriousness Criteria[b]**	**Outcome[c]**

	[a]CTCAE Grade	[b]Seriousness Criteria	[c]Outcome
Key:	1 = Grade 1 (mild) 2 = Grade 2 (moderate) 3 = Grade 3 (severe) 4 = Grade 4 (life-threatening) 5 = Grade 5 (fatal) Please indicate CTCAE version used.	D = Death LT = Life-threatening H = Initial or prolonged hospitalization S = Significant disability or incapacity M = Medically significant N/A = Not applicable (non-serious)	1 = Recovered/resolved 2 = Recovering/resolving 3 = Not recovered/not resolved 4 = Recovered/resolved with sequelae 5 = Fatal 6 = Unknown

If the event resulted in death, please provide the following information.

Date of death (dd/Mmm/yyyy): _____/_____/_____

Cause of death: _____

Was an autopsy performed? ☐ Yes ☐ No If yes, please provide the autopsy report if available.

If the event resulted in hospitalization, please provide the following information.

Admission date (dd/Mmm/yyyy): _____/_____/_____

Discharge date (dd/Mmm/yyyy): _____/_____/_____

Diagnostic Results - indicate N/A if not performed		
Date of Test (dd/Mmm/yyyy)	**Pathology: specify tissue type (including any additional analysis, molecular markers, etc.)**	**Imaging or Other Diagnostic Results**

Additional Questions

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Additional Event Information

Please indicate any pre-existing factors that may have contributed to the development of a secondary malignancy.

In your opinion, what is the causal relationship between the secondary malignancy and the CAR T therapy?

☐ Related ☐ Not related

If related, were alternate causes for the secondary malignancy ruled out? ☐ Yes ☐ No

If yes, please describe how these alternate causes were ruled out.

If not related, what was the cause of the secondary malignancy?

Were any treatments administered for the secondary malignancy? ☐ Yes ☐ No

If yes, please indicate treatment details below.

Name of Treatment	Route	Dose	Therapy Dates (dd/Mmm/yyyy)	Response

Relevant Medical History

If no relevant medical history, please indicate so here: ☐ No relevant medical history

Please include any prior cancer history with dates of diagnosis and stage of disease, specific agents of all cytotoxic chemotherapy or targeted therapy regimens, as well as therapeutic radiation exposure.

Diagnosis and Stage	Treatment Regimen	Therapy Dates (dd/Mmm/yyyy)	Response

Additional Questions

Please indicate any other risk factors for a secondary malignancy below.	
History of tobacco use? ☐ Yes ☐ No	If yes, please indicate number of pack-years:
History of environmental exposure (eg, asbestos, radiation)? ☐ Yes ☐ No	If yes, please describe:
History of hereditary cancer syndromes? ☐ Yes ☐ No	If yes, please describe:
Family history of cancer? ☐ Yes ☐ No	If yes, please describe:
Any other risk factors for a secondary malignancy? ☐ Yes ☐ No	If yes, please describe:

Concomitant Medications

Please list concomitant medications below. If the list is too long, please attach a printout of the patient's medications.

Drug Name	Indication	Dose/Frequency	Start Date (dd/Mmm/yyyy)	Stop Date (dd/Mmm/yyyy)

Please provide any supplemental information on a separate page.

Signature of Person Completing Form:	
Name of Person Completing Form (Print):	**Date Completed (dd/Mmm/yyyy):**
E-mail Address:	**Phone Number:**

Additional Questions

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ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Proposed Additional Risk Minimisation Measures:

Availability of tocilizumab and site qualification via the controlled distribution programme

The Marketing Authorisation Holder (MAH) will ensure that hospitals and their associated centres that dispense Breyanzi are qualified in accordance with the agreed controlled distribution programme by:

- ensuring immediate, on-site access to 1 dose of tocilizumab per patient prior to Breyanzi infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensuring that suitable alternative measures to treat CRS instead of tocilizumab are available on site;
- healthcare professionals (HCPs) involved in the treatment of a patient have completed the educational programme.

Educational Programme

HCP Educational Programme

All HCPs who are expected to prescribe, dispense, and administer Breyanzi shall be provided with an HCP guide, which will contain information about:

- identification of CRS and serious neurologic adverse reactions s including ICANS;
- management of CRS and serious neurologic adverse reactions including ICANS;
- adequate monitoring of CRS and serious neurologic adverse reactions including ICANS;
- provision of all relevant information to patients;
- ensuring immediate, on-site access to 1 dose of tocilizumab per patient prior to Breyanzi infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on site;
- risk of secondary malignancy of T-cell origin
- contact details for tumour sample testing after development of a secondary malignancy of T cell origin;
- provide information about the safety and efficacy long-term follow-up study and the importance of contributing to such a study;
- ensure that adverse reactions are adequately and appropriately reported;
- ensure that detailed instructions about the thawing procedure are provided.

Patient Educational Programme

All patients who receive Breyanzi shall be provided with a patient card, which will contain the following key messages:

- the risks of CRS and serious neurologic adverse reactions associated with Breyanzi;
- the need to report the symptoms of suspected CRS and neurotoxicity to their treating doctor immediately;
- the need to remain in the proximity of the location where Breyanzi was received for at least 2 weeks following Breyanzi infusion;
- the need to carry the patient card at all times;
- a reminder to patients to show the patient card to all HCPs, including in conditions of emergency, and a message for HCPs that the patient has been treated with Breyanzi;
- fields to record contact details of the prescriber and batch number.