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 (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.

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)
	Infections
	Hypogammaglobulinaemia
	Macrophage activation syndrome/haemophagocytic lymphohistiocytosis (MAS/HLH)
	Tumour lysis syndrome (TLS)
	Cytopenia, including bone marrow failure
Important potential risks	Autoimmune disorders
	Aggravation of graft versus host disease (GvHD)
	Secondary malignancies/insertional oncogenesis
	Cerebral oedema
	Generation of replication competent lentivirus (RCL)
	Immunogenicity

List of important risks and missing information

	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	CRS has been reported with all anti-cluster of differentiation (CD)19 directed chimeric antigen receptor (CAR) T therapeutics and is considered intrinsic to the therapeutic class. In Pooled 2L Treated Set, 45.2% of subjects experienced CRS. 29.9% of the events were mild and 14.1% of the events were moderate in severity. 2 (1.1%) events were Grade 3 with none being Grade 4 or fatal. In the Pooled 2L and 3L+ LBCL Treated Set, 41.8% of subjects experienced CRS. 26.0% of events were mild and 14.1% of the events were moderate in severity. 6 (1.0%) of the events were severe and 4 (0.7%) events were life-threatening in severity. CRS 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 the important identified risk of CRS. Analysis of adverse events (AEs) by Baseline Disease Characteristic showed that greater disease burden (ie, sum of products of diameter [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).
Risk minimization 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)

Important identified risks

	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)
Neurologic Toxicity (NT)	
Evidence for linking the risk to the medicine	Neurologic toxicity 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 toxicity is 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 adverse events (TEAEs) considered to be NT related to BREYANZI, and termed this finding investigator identified NT (iiNT). The maximum iiNT grade was determined by the highest grade of any component TEAE considered part of iiNT. In the Pooled 2L Treated Set, 18.1% of experienced iiNT. 9.6% were mild and 4.0% of the events were moderate in severity. 4.5% of the events were Grade 3 with none being Grade 4 or fatal. In the Pooled 2L and 3L+ LBCL Treated Set, 24.8% of subjects experienced iiNT. 8.6% were mild and 7.9% of the events were moderate in severity. 7.2% of the events were severe and 1.2% 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.
Risk factors and risk groups	Disease burden is a risk factor 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).
Risk minimization 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)

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 patients' risk for developing high grade and serious infections. In the Pooled 2L Treated Set, 10.2% of subjects experienced ≥ Grade 3 treatment-emergent infections. 7.3% were severe and 1.7% of the events were life-threatening in severity with 1.1% of the events being fatal. In the Pooled 2L and 3L+ LBCL Treated Set, 11.8% of liso-cel treated subjects had ≥ Grade 3 treatment-emergent infections. 8.6% were severe and 2.1% of the events were life-threatening in severity with 1.2% 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 minimization 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) 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 Pooled 2L Treated Set, 8.5% of subjects experienced hypogammaglobulinaemia. TEAEs of hypogammaglobulinaemia were noted in 6.8% of subjects in the treatment-emergent period and in 2.4% of subjects in the post treatment-emergent period. Grade ≥ 3 hypogammaglobulinaemia was reported in 0.6% of subjects in the treatment-emergent period and was not reported in any subjects in the post treatment-emergent period. In the Pooled 2L and 3L+ LBCL Treated Set, TEAEs of hypogammaglobulinaemia were noted in 10.7% of subjects in the treatment-emergent period and in 4.8% of subjects in the post treatment-emergent period. Grade ≥ 3 hypogammaglobulinaemia was reported in 0.2% subjects in the treatment-emergent period and was not reported in any subjects in the post treatment-emergent period.
Risk factors and risk groups	Prior treatment with rituximab and other drugs that can promote lymphopenia.
Risk minimization measures	**Routine Risk Minimisation Activities:** SmPC Section 4.4 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR **Additional Risk Minimisation Activities:** None

Important identified risks

Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005)
Macrophage Activation Syndrome/Haemophagocytic Lymphohistiocytosis (MAS/HLH)	
Evidence for linking the risk to the medicine	In the Pooled 2L Treated Set, 1.1% of subjects experienced a MAS/HLH event. (0.6%) of events were moderate in severity and 0.6% of events were fatal. In the Pooled 2L and 3L+ LBCL Treated Set, 0.7% of subjects experienced MAS/HLH events. 0.2% of events were moderate and 0.3% of the events were life-threatening in severity. 0.2% of the events were fatal.MAS/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 minimization 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), considered as part of the spectrum of CRS.
Tumour Lysis Syndrome (TLS)	
Evidence for linking the risk to the medicine	In the Pooled 2L Treated Set, no experienced TLS events. TLS was reported in 2 of 608 subjects (0.3%) in the Pooled 2L and 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 minimization 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)
Cytopenia, Including Bone Marrow Failure	
Evidence for linking the risk to the medicine	Prolonged cytopenia (laboratory values of haemoglobin, platelets or neutrophils ≥ Grade 3 Day 35 for BCM-003 and at Day 29 for Studies, 017001, 017006, 017007, BCM-001, and BCM-002) occurred in 62 subjects (35.0%) in the Pooled 2L Treated Set and 217 subjects (35.7%) in the Pooled 2L and 3L+ LBCL Treated Set. In the Pooled 2L Treated Set, , neutropenia (70.6%), anaemia (44.6%), and thrombocytopenia (42.9%) were the most commonly reported TEAEs in subjects. In the Pooled 2L and 3L+ LBCL Treated Set, the most frequent Grade ≥ 3 cytopenia AEs per PT neutropenia occurring in 409 subjects (67.3%), followed by anaemia in 275 subjects (45.2%), and thrombocytopenia occurring in

Important identified risks

	228 subjects (37.5%). In addition, Grade ≥ 3 cytopenia AEs of febrile neutropenia (8.6%), neutrophil count decreased (1.6%), pancytopenia (0.7%), bone marrow failure (0.5%), and platelet count decreased (0.5%) were reported.
Risk factors and risk groups	Previous anti-cancer therapy (chemotherapy, radiation) and LDC predispose to cytopenia.
Risk minimization 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) LTFU study (GC-LTFU-001)

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 minimization 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-haematopoietic stem cell transplant (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 Pooled 2L Treated Set, no subjects experienced an AE of GvHD. A Grade 1 AE of GvHD of bowel and skin was reported in the Pooled 2L and 3L+ LBCL Treated Set.
Risk factors and risk groups	Patients with active GvHD from prior HSCT.

Important potential risks

Risk minimization measures	**Routine Risk Minimisation Activities:** 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).
Secondary Malignancies/Insertional Oncogenesis	
Evidence for linking the risk to the medicine	In the Pooled 2L Treated Set, 1 of 177 subjects (0.6%) reported secondary malignancies 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). 5 of 167 subjects (3.0%) reported secondary malignancies during the post treatment-emergent period (period which starts from 91 days post the infusion of liso-cel). 1 (0.6%) event was fatal. In the Pooled 2L and 3L+ LBCL Treated Set, a total of 8 of 608 subjects (1.3%) reported secondary malignancies 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 29 of 559 subjects (5.2%) reported secondary malignancies during the post treatment-emergent period (period which starts from 91 days post the final infusion of BREYANZI). 5 (0.9%) events were fatal. Adverse events 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, no secondary malignancies due to insertional oncogenesis have been identified to date.
Risk factors and risk groups	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 minimization measures	**Routine Risk Minimisation Activities:** SmPC Section 4.4 – warnings, advice and management **Additional Risk Minimisation Activities:** None
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

Cerebral Oedema	
Evidence for linking the risk to the medicine	In the Pooled 2L Treated Set, no subjects reported events of cerebral oedema. In the Pooled 2L and 3L+ LBCL Treated Set, there is one reported case of cerebral oedema - a localised, unilateral, Grade 2 right temporal oedema reported in a subject who was later determined to have DLBCL involvement of the central nervous system (CNS). Serious and life-threatening reports of cerebral oedema have been reported after treatment with other CAR T products and CAR T product candidates.
Risk factors and risk groups	Risk factors and risk groups are unknown at this time but are presumed to be the same as those for neurotoxicity (ie, higher disease burden and higher inflammatory state and some have commented on overexpression of cytokines such as IFNgamma, TNFa, IL-1, and IL-6). Pre-existing extension of DLBCL to the CNS does not appear to be associated with a greater risk for cerebral oedema.
Risk minimization measures	**Routine Risk Minimisation Activities:** SmPC Section 4.4 – 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:** Included under the category of NT considered related to BREYANZI treatment in postauthorisation observational registry-based study (JCAR017-BCM-005).
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 minimization measures	**Routine Risk Minimisation Activities:** None **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001)

Important potential risks

Immunogenicity	
Evidence for linking the risk to the medicine	In the Pooled 2L Treated Set, 13.0% of subjects experienced AEs suggesting immunogenicity. 7.9% were mild and 4.5% of the events were moderate in severity. 0.6% of the events were ≥ Grade 3 with none being fatal. In the Pooled 2L and 3L+ LBCL Treated Set, 14.6% of subjects experienced AEs suggesting immunogenicity. 9.0% were mild and 5.1% of the events were moderate in severity. 0.5% of the events were ≥ Grade 3 with none being fatal. To be noted, AEs suggesting immunogenicity were reported in 19.8% of subjects in the SOC arm of 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 BREYANZI therapy, there have not been reports characteristic of anaphylaxis, angioedema or urticaria as sometimes observed in association with immunogenic biologic therapies.
Risk factors and risk groups	No known risk factors or risk groups.
Risk minimization 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.

Important potential risks

Risk minimization 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	
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 and 3L+ LBCL studies.
Risk factors and risk groups	No known risk factors or risk groups.
Risk minimization 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 minimization measures	**Routine Risk Minimization Measures:** SmPC Sections 4.2, PL Section 2 - warnings and advice **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) for pregnancy events. LTFU study (GC-LTFU-001)
Long-term Safety	
Risk minimization measures	**Routine Risk Minimization Measures:** None **Additional Risk Minimisation Activities:** None

Missing information

Additional activities	pharmacovigilance	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) LTFU study (GC-LTFU-001)
Safety in Patients < 18 years old		
Risk minimization measures		**Routine Risk Minimization Measures:** SmPC Section 4.2, PL Section 2 - warnings and advice **Additional Risk Minimisation Activities:** None
Additional activities	pharmacovigilance	**Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001).
Safety in Patients ≥ 75 years		
Risk minimization measures		**Routine Risk Minimization Measures:** None **Additional Risk Minimisation Activities:** None
Additional activities	pharmacovigilance	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005)

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:

Planned and ongoing post-authorization efficacy studies

Study short name and title	Summary of objectives
Efficacy studies which are conditions of the marketing authorization	
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 postmarketing 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 postmarketing setting. • To assess the BREYANZI safety and effectiveness profile in certain subgroups including but not limited to: – By large B-cell lymphoma subtypes (eg, follicular lymphoma grade 3B [FL3B], primary mediastinal B-cell lymphoma [PMBCL], DLBCL not otherwise specified, high grade B-cell lymphoma). – According to geographical regions (eg, Europe). – Subjects aged ≥ 75 years.

Planned and ongoing post-authorization efficacy studies

Study short name and title	Summary of objectives
Efficacy studies which are conditions of the marketing authorization	
	– Subjects with comorbid conditions (eg, renal impairment, reduced cardiac function). – Subjects with secondary central nervous system (CNS) involvement. – Subjects with Eastern Cooperative Oncology Group (ECOG) performance score ≥ 2. – By possible prognostic factors (eg, high-risk international prognostic index [IPI]). – Subjects previously exposed to anti-CD19 therapy. – Subjects with low pre-leukapheresis absolute lymphocyte count (< 0.3 × 109/L). – Subjects treated with out-of-specification product.
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.