



## **SUMMARY OF THE RISK MANAGEMENT PLAN FOR LISOCABTAGENE MARALEUCEL (BREYANZI®)**

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Based on European Union RMP Version 2.4

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### **Disclaimer:**

**The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Breyanzi® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, eg, by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Breyanzi® in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see [www.swissmedic.ch](http://www.swissmedic.ch)) approved and authorized by Swissmedic. Bristol-Myers Squibb SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of Breyanzi®**

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## **1 SUMMARY OF THE RISK MANAGEMENT PLAN**

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.

### **1.1 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: <https://www.ema.europa.eu/en/medicines/human/EPAR/breyanzi>

### **1.2 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.

### **1.2.1 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.

<b>List of Important Risks and Missing Information</b>	
<b>Important Identified Risks</b>	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
<b>Important Potential Risks</b>	Autoimmune disorders
	Aggravation of graft versus host disease (GvHD)
	Secondary malignancies/insertional oncogenesis
	Cerebral oedema
	Generation of replication competent lentivirus (RCL)
	Immunogenicity
	Transmission of infectious agents
Reduced viability of BREYANZI due to inappropriate product handling	
<b>Missing Information</b>	Impact on pregnancy and lactation
	Long-term safety
	Safety in patients < 18 years old
	Safety in patients ≥ 75 years

## 1.2.2 Summary of Important Risks

### Important Identified Risks

#### Cytokine Release Syndrome (CRS)

Evidence for Linking the Risk to the Medicine	<p>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.</p> <p>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.</p>
Risk Factors and Risk Groups	<p>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] <math>\geq 50</math> cm<sup>2</sup> by computed tomography [CT] scan or lactate dehydrogenase [LDH] <math>\geq 500</math> U/L), or baseline inflammatory state (ie, C-reactive protein [CRP] <math>\geq 20</math> 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 <math>\geq 50</math> cm<sup>2</sup>) or with more aggressive disease (HGBCL or subjects who required bridging chemotherapy).</p>
Risk Minimisation Measures	<p><b>Routine Risk Minimisation Activities:</b> 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)</p> <p><b>Additional Risk Minimisation Activities:</b> Educational programme for HCPs and patients Controlled Distribution Programme</p>
Additional Pharmacovigilance Activities	<p><b>Additional pharmacovigilance activities:</b> Postauthorisation safety study (PASS) (JCAR017-BCM-005)</p>

## Important Identified Risks

### Neurologic Toxicity (NT)

Evidence for Linking the Risk to the Medicine	<p>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.</p> <p>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).</p> <p>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.</p>
Risk Factors and Risk Groups	<p>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 <math>\geq</math> 50 cm<sup>2</sup> by CT scan or LDH <math>\geq</math> 500 U/L), or baseline inflammatory state (ie, CRP <math>\geq</math> 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 <math>\geq</math> 50 cm<sup>2</sup>) or with more aggressive disease (HGBCL or subjects who required bridging chemotherapy).</p>
Risk Minimisation Measures	<p><b>Routine Risk Minimisation Activities:</b></p> <p>SmPC Sections 4.2, 4.4 and 4.7, PL Sections 2 and 3 - warnings, advice and management discussed</p> <p>SmPC Section 4.8 and PL Section 4 - listed as an ADR</p> <p><b>Additional Risk Minimisation Activities:</b></p> <p>Educational programme for HCPs and patients</p> <p>Controlled Distribution Programme</p>
Additional Pharmacovigilance Activities	<p><b>Additional Pharmacovigilance Activities:</b></p> <p>PASS (JCAR017-BCM-005)</p>

### Infections

Evidence for Linking the Risk to the Medicine	<p>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 <math>\geq</math> 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 <math>\geq</math> 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.</p>
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### Important Identified Risks

Risk Factors and Risk Groups	There was a numerically higher percentage of subjects with Grade $\geq 3$ infection in those with Grade $\geq 3$ neutropenia prior to LDC (23.5%) than in those who had Grade $\leq 2$ neutropenia prior to LDC (11.5%) in Study 017001.
Risk Minimisation Measures	<p><b>Routine Risk Minimisation Activities:</b> SmPC Section 4.4, PL Section 2 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR</p> <p><b>Additional Risk Minimisation Activities:</b> None</p>
Additional Pharmacovigilance Activities	<p><b>Additional Pharmacovigilance Activities:</b> PASS (JCAR017-BCM-005) Long-term follow-up (LTFU) study (GC-LTFU-001)</p>

### 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 $\geq 3$ 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 $\geq 3$ 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 Minimisation Measures	<p><b>Routine Risk Minimisation Activities:</b> SmPC Section 4.4 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR</p> <p><b>Additional Risk Minimisation Activities:</b> None</p>
Additional Pharmacovigilance Activities	<p><b>Additional Pharmacovigilance Activities:</b> PASS (JCAR017-BCM-005)</p>

### 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.
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### Important Identified Risks

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	<p><b>Routine Risk Minimisation Activities:</b> SmPC Section 4.4 – warnings, advice and management discussed SmPC Section 4.8 – histiocytosis haematophagic listed as an ADR</p> <p><b>Additional Risk Minimisation Activities:</b> None</p>
Additional Pharmacovigilance Activities	<p><b>Additional Pharmacovigilance Activities:</b> PASS (JCAR017-BCM-005), considered as part of the spectrum of CRS.</p>
<b>Tumour Lysis Syndrome (TLS)</b>	
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 Minimisation Measures	<p><b>Routine Risk Minimisation Activities:</b> SmPC Section 4.8 and PL Section 4 - listed as an ADR</p> <p><b>Additional Risk Minimisation Activities:</b> None</p>
Additional Pharmacovigilance Activities	<p><b>Additional Pharmacovigilance Activities:</b> PASS (JCAR017-BCM-005)</p>
<b>Cytopenia, Including Bone Marrow Failure</b>	
Evidence for Linking the Risk to the Medicine	<p>Prolonged cytopenia (laboratory values of haemoglobin, platelets or neutrophils <math>\geq</math> 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.</p> <p>In the Pooled 2L Treated Set, neutropenia (70.6%), anaemia (44.6%), and thrombocytopenia (42.9%) were the most commonly reported TEAEs in subjects.</p> <p>In the Pooled 2L and 3L+ LBCL Treated Set, the most frequent Grade <math>\geq</math> 3 cytopenia AEs per PT neutropenia occurring in 409 subjects (67.3%), followed by anaemia in 275 subjects (45.2%), and thrombocytopenia occurring in 228 subjects (37.5%). In addition, Grade <math>\geq</math> 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.</p>
Risk Factors and Risk Groups	Previous anti-cancer therapy (chemotherapy, radiation) and LDC predispose to cytopenia.
Risk Minimisation Measures	<p><b>Routine Risk Minimisation Activities:</b> 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</p> <p><b>Additional Risk Minimisation Activities:</b> None</p>



### Important Identified Risks

Additional Pharmacovigilance Activities	<p><b>Additional Pharmacovigilance Activities:</b> PASS (JCAR017-BCM-005) LTFU study (GC-LTFU-001)</p>
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### 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	<p><b>Routine Risk Minimisation Activities:</b> None</p> <p><b>Additional Risk Minimisation Activities:</b> None</p>
Additional Pharmacovigilance Activities	<p><b>Additional Pharmacovigilance Activities:</b> LTFU study (GC-LTFU-001)</p>

#### Aggravation of Graft versus Host Disease (GvHD)

Evidence for Linking the Risk to the Medicine	<p>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.</p> <p>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.</p>
Risk Factors and Risk Groups	Patients with active GvHD from prior HSCT.
Risk Minimisation Measures	<p><b>Routine Risk Minimisation Activities:</b> SmPC Section 4.4, PL Section 2 – warnings, advice and management</p> <p><b>Additional Risk Minimisation Activities:</b> None</p>
Additional Pharmacovigilance Activities	<p><b>Additional pharmacovigilance activities:</b> Included under the category of Other AEs considered related to BREYANZI treatment in postauthorisation observational registry-based study (JCAR017-BCM-005).</p>

## Important Potential Risks

### Secondary Malignancies/Insertional Oncogenesis

Evidence for Linking the Risk to the Medicine	<p>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.</p> <p>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.</p> <p>Based on the tumour samples received and tested, no secondary malignancies due to insertional oncogenesis have been identified to date.</p>
Risk Factors and Risk Groups	<p>Patients with DLBCL have an increased risk of developing secondary malignancies related to prior chemotherapy, particularly for MDS and AML.</p> <p>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.</p>
Risk Minimisation Measures	<p><b>Routine Risk Minimisation Activities:</b> SmPC Section 4.4 - warnings, advice and management</p> <p><b>Additional Risk Minimisation Activities:</b> None</p>
Additional Pharmacovigilance Activities	<p><b>Additional Pharmacovigilance Activities:</b> PASS (JCAR017-BCM-005) LTFU study (GC-LTFU-001) Transgene assay service testing of secondary malignancies with insertion site analysis as applicable</p>

### Cerebral Oedema

Evidence for Linking the Risk to the Medicine	<p>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).</p> <p>Serious and life-threatening reports of cerebral oedema have been reported after treatment with other CAR T products and CAR T product candidates.</p>
Risk Factors and Risk Groups	<p>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 IFN<math>\gamma</math>, TNF<math>\alpha</math>, 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.</p>

### Important Potential Risks

Risk Minimisation Measures	<p><b>Routine Risk Minimisation Activities:</b> SmPC Section 4.4 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR</p> <p><b>Additional Risk Minimisation Activities:</b> None</p>
Additional Pharmacovigilance Activities	<p><b>Additional Pharmacovigilance Activities:</b> Included under the category of NT considered related to BREYANZI treatment in postauthorisation observational registry-based study (JCAR017-BCM-005).</p>
<b>Generation of Replication Competent Lentivirus</b>	
Evidence for Linking the Risk to the Medicine	<p>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.</p>
Risk Factors and Risk Groups	<p>No known risk factors or risk groups.</p>
Risk Minimisation Measures	<p><b>Routine Risk Minimisation Activities:</b> None</p> <p><b>Additional Risk Minimisation Activities:</b> None</p>
Additional Pharmacovigilance Activities	<p><b>Additional Pharmacovigilance Activities:</b> LTFU study (GC-LTFU-001)</p>
<b>Immunogenicity</b>	
Evidence for Linking the Risk to the Medicine	<p>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 <math>\geq</math> 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 <math>\geq</math> 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 <math>\geq</math> Grade 3 and was life-threatening in severity.</p> <p>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-boostered 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.</p> <p>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.</p>

### Important Potential Risks

	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 Minimisation Measures	<p><b>Routine Risk Minimisation Activities:</b> 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</p> <p><b>Additional Risk Minimisation Activities:</b> None</p>
Additional Pharmacovigilance Activities	<p><b>Additional Pharmacovigilance Activities:</b> None</p>
<b>Transmission of Infectious Agents</b>	
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 <i>Staphylococcus epidermidis</i> 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	<p><b>Routine Risk Minimisation Activities:</b> 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</p> <p><b>Additional Risk Minimisation Activities:</b> None</p>
Additional Pharmacovigilance Activities	<p><b>Additional Pharmacovigilance Activities:</b> None</p>
<b>Reduced Viability of BREYANZI due to Inappropriate Product Handling</b>	
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 Minimisation Measures	<p><b>Routine Risk Minimisation Activities:</b> SmPC Sections 4.2, 6.3, 6.4, 6.5 and 6.6, PL Section 5 and Labelling Section 9 - handling instructions</p> <p><b>Additional Risk Minimisation Activities:</b> Educational programme for HCPs Controlled Distribution Programme</p>

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### Important Potential Risks

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Additional Pharmacovigilance Activities	<b>Additional Pharmacovigilance Activities:</b> None
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### Missing Information

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#### Impact on Pregnancy and Lactation

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Risk Minimisation Measures	<b>Routine Risk Minimisation Measures:</b> SmPC Section 4.6, PL Section 2 - warnings and advice  <b>Additional Risk Minimisation Activities:</b> None
Additional Pharmacovigilance Activities	<b>Additional Pharmacovigilance Activities:</b> PASS (JCAR017-BCM-005) for pregnancy events. LTFU study (GC-LTFU-001)

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#### Long-term Safety

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Risk Minimisation Measures	<b>Routine Risk Minimisation Measures:</b> None  <b>Additional Risk Minimisation Activities:</b> None
Additional Pharmacovigilance Activities	<b>Additional Pharmacovigilance Activities:</b> PASS (JCAR017-BCM-005) LTFU study (GC-LTFU-001)

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#### Safety in Patients < 18 Years

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Risk Minimisation Measures	<b>Routine Risk Minimisation Measures:</b> SmPC Section 4.2, PL Section 2 - warnings and advice  <b>Additional Risk Minimisation Activities:</b> None
Additional Pharmacovigilance Activities	<b>Additional Pharmacovigilance Activities:</b> LTFU study (GC-LTFU-001).

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#### Safety in Patients ≥ 75 years

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Risk Minimisation Measures	<b>Routine Risk Minimisation Measures:</b> None  <b>Additional Risk Minimisation Activities:</b> None
Additional Pharmacovigilance Activities	<b>Additional Pharmacovigilance Activities:</b> PASS (JCAR017-BCM-005)

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### 1.2.3 **Post-authorisation Development Plan**

#### 1.2.3.1 **Studies Which Are Conditions of the Marketing Authorisation**

The following studies are conditions of the marketing authorisation:

##### **Planned and Ongoing Post-authorization Efficacy Studies**

<b>Study Short Name and Title</b>	<b>Summary of Objectives</b>
<b>Efficacy Studies Which Are Conditions of the Marketing Authorization</b>	
Postauthorisation Safety Study JCAR017-BCM-005	<p><u>Primary Objective:</u> 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.</p> <p><u>Secondary Objectives:</u></p> <ul style="list-style-type: none"> <li>• To assess long-term effectiveness in patients treated with BREYANZI in the postmarketing setting.</li> <li>• To assess the BREYANZI safety and effectiveness profile in certain subgroups including but not limited to: <ul style="list-style-type: none"> <li>– 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).</li> <li>– According to geographical regions (eg, Europe).</li> <li>– Subjects aged <math>\geq 75</math> years.</li> <li>– Subjects with comorbid conditions (eg, renal impairment, reduced cardiac function).</li> <li>– Subjects with secondary central nervous system (CNS) involvement.</li> <li>– Subjects with Eastern Cooperative Oncology Group (ECOG) performance score <math>\geq 2</math>.</li> <li>– By possible prognostic factors (eg, high-risk international prognostic index [IPI]).</li> <li>– Subjects previously exposed to anti-CD19 therapy.</li> <li>– Subjects with low pre-leukapheresis absolute lymphocyte count (<math>&lt; 0.3 \times 10^9/L</math>).</li> <li>– Subjects treated with out-of-specification product.</li> </ul> </li> </ul>
Study 017001: 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	<p><u>Primary Objectives:</u></p> <ul style="list-style-type: none"> <li>• To evaluate the safety of JCAR017 in adult subjects with R/R B-cell NHL.</li> <li>• To assess the antitumour activity of JCAR017.</li> </ul> <p><u>Secondary Objectives:</u></p> <ul style="list-style-type: none"> <li>• To assess the rate of CR and durability of antitumour activity of JCAR017.</li> <li>• To estimate the PFS and OS of subjects treated with JCAR017.</li> <li>• To characterize the PK profile of JCAR017.</li> <li>• To assess HRQoL and HEOR.</li> </ul>

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**Planned and Ongoing Post-authorization Efficacy Studies**

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**Study Short Name and Title    Summary of Objectives**

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**Efficacy Studies Which Are Conditions of the Marketing Authorization**

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JCAR017-BCM-001 (Cohort 1)	<p><u>Exploratory Objectives:</u></p> <ul style="list-style-type: none"><li>• To assess the effect of JCAR017 on antitumor activity using Bayesian methods.</li><li>• To assess immune responses to JCAR017.</li><li>• To assess the pharmacodynamic effects of JCAR017.</li></ul> <p><u>Primary Objective:</u></p> <ul style="list-style-type: none"><li>• To determine the efficacy, defined as ORR of JCAR017 in subjects with aggressive B-cell NHL.</li></ul> <p><u>Secondary Objectives:</u></p> <ul style="list-style-type: none"><li>• To evaluate the safety and feasibility of administering JCAR017.</li><li>• To evaluate other measures of efficacy of JCAR017 (eg, CRR, EFS, PFS, OS, DOR).</li><li>• To characterize the PK profile of JCAR017 in the peripheral blood measured using qPCR detection for the JCAR017 vector sequence.</li><li>• To describe changes in HRQoL using the global health/QoL, fatigue, physical and cognitive functioning subscales of the EORTC QLQ-C30 and the FACT-LymS.</li></ul> <p><u>Exploratory Objectives:</u></p> <ul style="list-style-type: none"><li>• To characterize the PK profile of JCAR017 in the peripheral blood flow cytometry.</li><li>• To evaluate pharmacodynamic (PD) markers of JCAR017, including soluble factors such as chemokines and cytokines.</li><li>• To evaluate clinical outcomes versus histologies, disease characteristics and subject characteristics. To evaluate the tumour and tumour microenvironment for mechanisms of response and resistance to JCAR017.</li><li>• To evaluate the tumor and tumor microenvironment for mechanisms of response and resistance to JCAR017.</li><li>• To describe the effect of treatments directed at severe cytokine release syndrome (sCRS) and neurotoxicity on duration and severity of these events.</li><li>• To describe JCAR017 PK and PD effects on JCAR07 cell persistence and on the response of JCAR017 treatment of the disease under study.</li><li>• To characterize the prevalence and incidence of humoral immune responses to JCAR017.</li><li>• To characterize the subject experience on JCAR017 using patient interviews.</li><li>• To measure hospital resource utilization, including hospitalization rate.</li><li>• To describe changes in the other domains of HRQoL using the rest of subscales in EORTC QLQ-C30 questionnaire (ie, those not specified in the secondary objectives).</li><li>• To describe changes in health utility scores and global health using the European Quality of Life-5 Dimension health state classifier to 5 Levels (EQ-5D-5L).</li></ul>
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**Planned and Ongoing Post-authorization Efficacy Studies**

<b>Study Short Name and Title</b>	<b>Summary of Objectives</b>
<b>Efficacy Studies Which Are Conditions of the Marketing Authorization</b>	
Study CA082-1105 (Batch analysis with clinical outcomes from JCAR017-BCM-005)	<ul style="list-style-type: none"> <li>To assess the consistency of product quality and clinical outcomes.</li> </ul>
<b>Efficacy Studies Which Are Specific Obligations</b>	
None	NA

**1.2.3.2 Other Studies in Post-authorization Development Plan**

**Category 3 Ongoing and Planned Additional Pharmacovigilance Activities**

<b>Study Short Name and Title</b>	<b>Rationale and Study Objectives</b>
Long-term Follow-up Study (Study GC-LTFU-001)	<p>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.</p> <p><u>Primary Objectives:</u></p> <ul style="list-style-type: none"> <li>To assess the risk of delayed AEs following exposure to gene modified (GM) T cells.</li> <li>To monitor for long-term persistence of GM T cells, including analysis of vector integration sites, as appropriate.</li> <li>To monitor for generation of replication competent retroviruses (RCR).</li> <li>To assess long-term efficacy following treatment with GM T cells.</li> <li>Describe growth and sexual maturity status for subjects who were aged &lt; 18 years at time of GM T cell treatment.</li> </ul> <p><u>Secondary Objective:</u></p> <ul style="list-style-type: none"> <li>To assess long term HRQoL following treatment with GM T cells.</li> </ul>