ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Breyanzi 1.1-70 x 10^6 cells/mL / 1.1-70 x 10^6 cells/mL dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Breyanzi (lisocabtagene maraleucel) is a CD19-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 CD3 zeta (ζ) chain signalling domains and a nonfunctional truncated epidermal growth factor receptor (EGFRt).

2.2 Qualitative and quantitative composition

Breyanzi contains CAR-positive viable T-cells, consisting of a defined composition of CD8+ and CD4+ cell components:

CD8+ cell 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-positive viable T-cells). The medicinal product is packaged in one or more vials containing a cell dispersion of 5.1-322 x 10^6 CAR-positive viable T-cells (1.1-70 x 10^6 CAR-positive viable T-cells/mL) suspended in a cryopreservative solution.

Each vial contains 4.6 mL of CD8+ cell component.

CD4+ cell 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-positive viable T-cells). The medicinal product is packaged in one or more vials containing a cell dispersion of 5.1-322 x 10^6 CAR-positive viable T-cells (1.1-70 x 10^6 CAR-positive 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 Breyanzi. The total volume to be dosed and the number of vials required may differ for each cell component.

The quantitative information for each cell component of the medicinal product, including the number of vials (see section 6) to be administered, is presented in the release for infusion certificate (RfIC) located inside the lid of the cryoshipper used for transport. The RfIC for each component includes the total volume to be dosed, the number of vials required and the volume to be dosed from each vial, based on the cryopreserved CAR-positive viable T-cell concentration.

Excipients with known effect:

This medicinal product contains 12.5 mg sodium, 6.5 mg potassium, and 0.35 mL (7.5% v/v) dimethyl sulfoxide per vial (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion (infusion).

Slightly opaque to opaque, colourless to yellow, or brownish-yellow dispersion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breyanzi is indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy.

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory DLBCL, PMBCL and FL3B, after two or more lines of systemic therapy.

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

4.2 Posology and method of administration

Breyanzi must be administered in a qualified treatment centre.

Treatment should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with Breyanzi.

At least 1 dose of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available per patient prior to infusion of Breyanzi. 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, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.

Posology

Breyanzi is intended for autologous use (see section 4.4).

Treatment consists of a single dose for infusion containing a dispersion for infusion of CAR-positive viable T-cells in one or more vials.

The target dose is 100 x 10^6 CAR-positive viable T-cells (consisting of a target 1:1 ratio of CD4+ and CD8+ cell components) within a range of 44-120 x 10^6 CAR-positive viable T-cells. See the accompanying release for infusion certificate (RfIC) for additional information pertaining to dose.

The availability of Breyanzi must be confirmed before starting lymphodepleting chemotherapy regimen.

Patients should be clinically re-assessed prior to administration of lymphodepleting chemotherapy and Breyanzi to ensure no reasons to delay therapy (see section 4.4).

Pre-treatment (lymphodepleting chemotherapy)
Lymphodepleting chemotherapy consisting of cyclophosphamide 300 mg/m^2/day and fludarabine 30 mg/m^2/day, administered intravenously for three days. See the prescribing information for fludarabine and cyclophosphamide for information on dose adjustment in renal impairment.

Breyanzi is to be administered 2 to 7 days after completion of lymphodepleting chemotherapy.

If there is a delay of more than 2 weeks between completing lymphodepleting chemotherapy and the infusion of Breyanzi, then the patient should be re-treated with lymphodepleting chemotherapy prior to receiving the infusion (see section 4.4).

Pre-medication
It is recommended that premedication with paracetamol and diphenhydramine (25-50 mg, intravenously or orally) or another H1-antihistamine, be administered 30 to 60 minutes before the infusion of Breyanzi to reduce the possibility of an infusion reaction.

Prophylactic use of systemic corticosteroids should be avoided, as the use may interfere with the activity of Breyanzi (see section 4.4).

Monitoring after infusion

- Patients should be monitored 2-3 times during the first week following infusion, for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation at the first signs or symptoms of CRS and/or neurologic events.

- Frequency of monitoring after the first week should be carried out at the physician's discretion and should be continued for at least 2 weeks after infusion.

- Patients should be instructed to remain within proximity of a qualified treatment centre for at least 2 weeks following infusion.

<u>Special populations</u>

Patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection
There is no clinical experience in patients with active HIV, HBV or HCV 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 accepted for manufacturing (see section 4.4).

Renal impairment
There is no clinical experience in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min).

Elderly
No dose adjustment is required in patients over 65 years of age.

Paediatric population
The safety and efficacy of Breyanzi in children and adolescents below 18 years of age have not yet been established.

Method of administration

Breyanzi is for intravenous use only.

Preparation of Breyanzi
Before thawing the vials, it must be confirmed that the patient's identity matches the unique patient identifiers on the shipper, external carton and the release for infusion certificate (RfIC). The total number of vials to be administered must also be confirmed with the patient-specific label information on the release for infusion certificate (RfIC) (see section 4.4). The company must be contacted immediately if there are any discrepancies between the labels and the patient identifiers.

Administration
- **Do NOT** use a leukodepleting filter.
- Ensure tocilizumab or suitable alternatives, in the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, and emergency equipment are available prior to infusion and during the recovery period.
- Confirm the patient's identity matches the patient identifiers on the syringe label supplied on the respective release for infusion certificate (RfIC).
- Once Breyanzi components have been drawn into syringes, proceed with administration as soon as possible. The total time from removal from frozen storage to patient administration should not exceed 2 hours.

For detailed instructions on preparation, administration, measures to take in case of accidental exposure and disposal of Breyanzi, see section 6.6.

4.3 Contraindications

Hypersensitivity to any of the excipients listed in section 6.1.

Contraindications of the lymphodepleting chemotherapy must be considered.

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability, the name of the product, the batch number and the name of the treated patient must be kept for a period of 30 years after expiry date of the product.

Autologous use

Breyanzi is intended solely for autologous use and must not, under any circumstances, be administered to other patients. Breyanzi must not be administered if the information on the product labels and release for infusion certificate (RfIC) do not match the patient's identity.

Reasons to delay treatment

Due to the risks associated with Breyanzi treatment, infusion should be delayed if a patient has any of the following conditions:
- Unresolved serious adverse events (especially pulmonary events, cardiac events, or hypotension), including those after preceding chemotherapies.
- Active uncontrolled infections, or inflammatory disorders.
- Active graft-versus-host disease (GVHD).

In case of delayed Breyanzi infusion, see section 4.2.

Blood, organ, tissue and cell donation

Patients treated with Breyanzi must not donate blood, organs, tissues and cells for transplantation.

Central nervous system (CNS) lymphoma

There is no experience of use of Breyanzi in patients with primary CNS lymphoma. There is limited clinical experience of use of Breyanzi for secondary CNS lymphoma (see section 5.1).

Prior treatment with an anti-CD19 therapy

There is limited clinical experience with Breyanzi in patients exposed to prior CD19-directed therapy (see section 5.1). There are limited clinical data available on CD19-negative patients treated with Breyanzi. Patients with CD19-negative status by immunohistochemistry may still express CD19. The potential risks and benefits associated with treatment of CD19-negative patients with Breyanzi should be considered.

Cytokine release syndrome

CRS including fatal or life-threatening reactions can occur following Breyanzi infusion. For patients who received one prior line of therapy for large B-cell lymphoma (LBCL), the median time to onset was 4 days (range: 1 to 63 days, with the upper limit due to CRS onset, without fever, reported in one patient). For patients who received two or more prior lines of therapy for LBCL, the median time to onset was 4 days (range: 1 to 14 days). For patients who received Breyanzi for FL, the median time to onset was 6 days (range: 1 to 17 days). For patients who received Breyanzi for MCL, the median time to onset was 4 days (range: 1 to 10 days). Less than half of all patients treated with Breyanzi experienced some degree of CRS (see section 4.8).

In clinical studies, high tumour burden prior to Breyanzi infusion was associated with a higher incidence of CRS.

Tocilizumab and/or a corticosteroid were used to manage CRS after infusion of Breyanzi (see section 4.8).

Monitoring and management of CRS
CRS should be identified based on clinical presentation. Patients should be evaluated for and treated for other causes of fever, hypoxia, and hypotension.

At least one dose of tocilizumab must be available per patient on site prior to infusion of Breyanzi. The treatment centre should 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, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS. Patients should be monitored 2-3 times during the first week following Breyanzi infusion at the qualified treatment centre for signs and symptoms of CRS. Frequency of monitoring after the first week should be carried out at the physician’s discretion and should be continued for at least 2 weeks after infusion. Patients and caregivers should be informed about the potential late onset of CRS and instructed to seek immediate medical attention if patients experience any signs or symptoms of CRS.

At the first sign of CRS, treatment with supportive care, tocilizumab or tocilizumab and corticosteroids should be instituted as indicated in Table 1. Breyanzi continues to expand following administration of tocilizumab and corticosteroids (see section 5.2).

Patients who experience CRS should be closely monitored for cardiac and organ functioning until resolution of symptoms. For severe or life-threatening CRS, intensive care unit level monitoring and supportive therapy should be considered.

Evaluation for haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) should be considered in patients with severe or unresponsive CRS. Treatment of HLH/MAS should be administered per institutional guidelines.

If concurrent neurologic toxicity is suspected during CRS, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2
- Tocilizumab according to the CRS grade in Table 1
- Anti-seizure medication according to the neurologic toxicity grade in Table 2.

Table 1: CRS grading and management guidance

CRS grade[a]	**Tocilizumab**	**Corticosteroids**[b]
Grade 1 Fever	If 72 hours or more after infusion, treat symptomatically. If less than 72 hours after infusion, consider tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).	If 72 hours or more after infusion, treat symptomatically. If less than 72 hours after infusion, consider dexamethasone 10 mg IV every 24 hours.
Grade 2 Symptoms require and respond to moderate intervention. Fever, oxygen requirement less than 40% fraction of inspired oxygen (FiO_2), or hypotension responsive to fluids or low dose of one vasopressor, or Grade 2 organ toxicity.	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).	If 72 hours or more after infusion, consider dexamethasone 10 mg IV every 12-24 hours. If less than 72 hours after infusion, administer dexamethasone 10 mg IV every 12-24 hours.
	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (10-20 mg IV every 6 to 12 hours). If no improvement or continued rapid progression, maximise dexamethasone, switch to high-dose methylprednisolone 2 mg/kg if needed. After 2 doses of tocilizumab, consider alternative immunosuppressants. Do not exceed 3 doses tocilizumab in 24 hours, or 4 doses in total.	

CRS grade[a]	Tocilizumab	Corticosteroids[b]
Grade 3 Symptoms require and respond to aggressive intervention. Fever, oxygen requirement greater than or equal to 40% FiO_2, or hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity, or Grade 4 transaminitis.	Per Grade 2.	Administer dexamethasone 10 mg IV every 12 hours.
	If no improvement within 24 hours or rapid progression of CRS, escalate tocilizumab and corticosteroid use as per Grade 2.	
Grade 4 Life-threatening symptoms. Requirements for ventilator support or continuous veno-venous haemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2.	Administer dexamethasone 20 mg IV every 6 hours.
	If no improvement within 24 hours or rapid progression of CRS, escalate tocilizumab and corticosteroid use as per Grade 2.	

[a] Lee *et al* 2014.
[b] If corticosteroids are initiated, continue for at least 3 doses or until complete resolution of symptoms, and consider corticosteroid taper.

Neurologic adverse reactions

Neurologic toxicities, including immune effector cell-associated neurotoxicity syndrome (ICANS), which may be fatal or life-threatening, occurred following treatment with Breyanzi, including concurrently with CRS, after CRS resolution, or in the absence of CRS. For patients who received one prior line of therapy for LBCL, the median time to onset of the first event was 8 days (range: 1 to 63 days), for patients who received two or more prior lines of therapy for LBCL, the median time to onset of the first event was 9 days (range: 1 to 66 days), for patients who received Breyanzi for FL, the median time to onset of the first event was 8 days (range: 4 to 16 days) , and for patients who received Breyanzi for MCL, the median time to onset of the first event was 8 days (range: 1 to 25 days). The most common neurologic symptoms included encephalopathy, tremor, aphasia, delirium, dizziness and headache (see section 4.8).

Monitoring and management of neurologic toxicities
Patients should be monitored 2-3 times during the first week following infusion, at the qualified treatment centre for signs and symptoms of neurologic toxicities. Frequency of monitoring after the first week should be carried out at the physician's discretion and should be continued for at least 2 weeks after infusion. Patients and caregivers should be informed about the potential late onset of neurologic toxicities and instructed to seek immediate medical attention if patients experience any signs or symptoms of neurologic toxicities.

If neurologic toxicity is suspected, it is to be managed according to the recommendations in Table 2. Other causes of neurologic symptoms should be ruled out, including vascular events. Intensive care supportive therapy should be provided for severe or life-threatening neurologic toxicities.

If concurrent CRS is suspected during the neurologic toxicity administer:
- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2
- Tocilizumab according to the CRS grade in Table 1
- Antiseizure medication according to the neurologic toxicity grade in Table 2.

Table 2: Neurologic toxicity (NT) / including ICANS grading and management guidance

Neurologic toxicity grade including presenting symptoms[a]	Corticosteroids and anti-seizure medication

Neurologic toxicity grade including presenting symptoms[a]	Corticosteroids and anti-seizure medication
Grade 1* Mild or asymptomatic. or ICE score 7-9[b] or Depressed level of consciousness[c]: awakens spontaneously.	Start non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. If 72 hours or more after infusion, observe. If less than 72 hours after infusion, dexamethasone 10 mg IV every 12 to 24 hours for 2-3 days.
Grade 2* Moderate. or ICE score 3-6[b] or Depressed level of consciousness[c]: awakens to voice.	Start non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 10 mg IV every 12 hours for 2-3 days, or longer for persistent symptoms. Consider taper for a total corticosteroid exposure of greater than 3 days. If no improvement after 24 hours or worsening of neurologic toxicity, increase the dose and/or frequency of dexamethasone up to maximum of 20 mg IV every 6 hours. If no improvement after another 24 hours, rapidly progressing symptoms, or life-threatening complications arise, give methylprednisolone (2 mg/kg loading dose, followed by 2 mg/kg divided 4 times a day; taper within 7 days).
Grade 3* Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation; disabling. or ICE score 0-2[b] *if ICE score is 0, but the patient is arousable (e.g., awake with global aphasia) and able to perform assessment.* or Depressed level of consciousness[c]: awakens only to tactile stimulus, or seizures[c], either: • any clinical seizure, focal or generalised, that resolves rapidly, or • non-convulsive seizures on EEG that resolve with intervention, or raised ICP[c]: focal/local oedema on neuroimaging.	Start non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 10 to 20 mg IV every 8 to 12 hours. Corticosteroids are not recommended for isolated Grade 3 headaches. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to methylprednisolone (dose and frequency as per Grade 2). If cerebral oedema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated), and cyclophosphamide 1.5 g/m^2.

Neurologic toxicity grade including presenting symptoms[a]	**Corticosteroids and anti-seizure medication**
Grade 4* Life-threatening. or ICE score[b] 0 or Depressed level of consciousness[c], either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures[c], either: • life-threatening prolonged seizure (> 5 min), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[c]: • deep focal motor weakness such as hemiparesis or paraparesis, or, raised ICP/cerebral oedema[c], with signs/symptoms such as: • diffuse cerebral oedema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilledema, or • Cushing's triad.	Start non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 20 mg IV every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to methylprednisolone (dose and frequency as per Grade 2). If cerebral oedema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated), and cyclophosphamide 1.5 g/m^2.

EEG=Electroencephalogram; ICE = Immune effector cell-associated encephalopathy; ICP = Intracranial pressure.
*Grading per NCI CTCAE or ASTCT/ICANS
[a] Management is determined by the most severe event, not attributable to any other cause.
[b] If patient is arousable and able to perform ICE Assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (name 3 objects, e.g., point to clock, pen, button = 3 points); Following Commands (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.
[c] Attributable to no other cause.

Infections and febrile neutropenia

Breyanzi should not be administered to patients with a clinically significant active infection or inflammatory disorder. Severe infections including life-threatening or fatal infections, have occurred in patients after receiving this medicinal product (see section 4.8). Patients should be monitored for signs and symptoms of infection before and after administration and treated appropriately. Prophylactic anti-microbials should be administered according to standard institutional guidelines.

Febrile neutropenia has been observed in patients after treatment with Breyanzi (see section 4.8) and may be concurrent with CRS. In the event of febrile neutropenia, infection should be evaluated and managed with broad-spectrum antibiotics, fluids and other supportive care as medically indicated.

Patients treated with Breyanzi may be at an increased risk of severe/fatal COVID-19 infections. Patients should be counselled on the importance of prevention measures.

Viral reactivation

Viral reactivation, (e.g., HBV, human herpesvirus 6 [HHV-6] and John Cunningham [JC] virus) may occur in immunosuppressed patients.

Viral reactivation manifestations may complicate and delay the diagnosis and appropriate treatment of CAR T-cell-related adverse events. Appropriate diagnostic evaluations should be performed to help differentiate these manifestations from CAR T-cell-related adverse events.

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with medicinal products directed against B-cells. For patients with a prior history of HBV, prophylactic antiviral suppressive therapy is recommended to prevent HBV reactivation during and after Breyanzi therapy (see section 5.1).

Reactivation of JC virus, leading to progressive multifocal leukoencephalopathy (PML), has been reported in patients treated with Breyanzi who have also received prior treatment with other immunosuppressive medicinal products. Cases with fatal outcome have been reported.

Serological testing

Screening for HBV, HCV, and HIV should be performed before collection of cells for manufacturing. (see section 4.2).

Prolonged cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Breyanzi (see section 4.8). Blood counts should be monitored prior to and after Breyanzi administration. Prolonged cytopenias should be managed according to clinical guidelines.

Hypogammaglobulinaemia

B-cell aplasia leading to hypogammaglobulinaemia can occur in patients receiving treatment with Breyanzi. Hypogammaglobulinaemia has been very commonly observed in patients treated with Breyanzi (see section 4.8). Immunoglobulin levels should be monitored after treatment and managed per clinical guidelines including infection precautions, antibiotic prophylaxis and/or immunoglobulin replacement.

Secondary malignancies including of T-cell origin

Patients treated with Breyanzi may develop secondary malignancies. T-cell malignancies have been reported following treatment of haematological malignancies with a BCMA- or CD19-directed CAR T-cell therapy, including Breyanzi. T-cell malignancies, including CAR-positive malignancies, have been reported within weeks and up to several years following administration of a CD19- or BCMA-, directed CAR T-cell therapy. There have been fatal outcomes. Patients should be monitored life-long for secondary malignancies. In the event that a secondary malignancy of T-cell origin occurs, the company should be contacted to obtain instructions on the collection of tumour samples for testing.

Tumour lysis syndrome (TLS)

TLS may occur in patients treated with CAR T therapies. To minimise the risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to Breyanzi infusion. Signs and symptoms of TLS should be monitored and managed in accordance with clinical guidelines.

Hypersensitivity reactions

Allergic reactions may occur with the infusion of Breyanzi. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide.

Transmission of an infectious agent

Although Breyanzi is tested for sterility and mycoplasma, a risk of transmission of infectious agents exists. Healthcare professionals administering Breyanzi must, therefore, monitor patients for signs and symptoms of infections after treatment and treat appropriately, if needed.

Interference with virological testing
Due to limited and short spans of identical genetic information between the lentiviral vector used to create Breyanzi and HIV, some HIV nucleic acid tests (NAT) may give a false positive result.

Prior stem cell transplantation (GVHD)

It is not recommended that patients who underwent an allogeneic stem cell transplant and suffer from active acute or chronic GVHD receive treatment because of the potential risk of Breyanzi worsening GVHD.

Long-term follow-up

Patients are expected to be enrolled in a registry and will be followed in the registry in order to better understand the long-term safety and efficacy of Breyanzi.

Excipients

This medicinal product contains 12.5 mg sodium per vial, equivalent to 0.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicinal product contains 0.2 mmol (or 6.5 mg) potassium per vial. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed in humans.

Monoclonal antibodies directed against the epidermal growth factor receptor (anti-EGFR mabs)

Long-term persistence of CAR T-cells may be affected by the subsequent use of anti-EGFR mabs however, there is limited information available on the clinical use of anti-EGFR mabs in patients treated with Breyanzi.

Live vaccines

The safety of immunisation with live viral vaccines during or following treatment with Breyanzi has not been studied. As a precautionary measure, vaccination with live vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Breyanzi treatment, and until immune recovery following treatment.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Pregnancy status for women of child-bearing potential should be verified using a pregnancy test prior to starting treatment with Breyanzi.

See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with Breyanzi.

Pregnancy

There are no data from the use of lisocabtagene maraleucel in pregnant women. No animal reproductive and developmental toxicity studies have been conducted to assess whether it can cause foetal harm when administered to a pregnant woman (see section 5.3).

It is not known if lisocabtagene maraleucel has the potential to be transferred to the foetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause foetal toxicity, including B-cell lymphocytopenia. Therefore, Breyanzi is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised on the potential risks to the foetus. Pregnancy after Breyanzi therapy should be discussed with the treating physician.

Assessment of immunoglobulin levels and B-cells in newborns of mothers treated with should be considered.

Breast-feeding

It is unknown whether lisocabtagene maraleucel is excreted in human milk or transferred to the breast-feeding child. Women who are breast-feeding should be advised of the potential risk to the breast-fed child.

Fertility

There are no data on the effect of lisocabtagene maraleucel on fertility.

4.7 Effects on ability to drive and use machines

Breyanzi may have major influence on the ability to drive and use machines.

Due to the potential for neurologic events, including altered mental status or seizures with Breyanzi, patients receiving Breyanzi should refrain from driving or operating heavy or potentially dangerous machines for at least 4 weeks after Breyanzi infusion, or longer at the physician's discretion.

4.8 Undesirable effects

Summary of the safety profile

LBCL

Patients who received one prior line of therapy for LBCL
The adverse reactions described in this section were characterised in 177 patients infused with Breyanzi from 3 pooled studies TRANSFORM [BCM-003], PILOT [017006], and TRANSCEND WORLD [JCAR017-BCM-001, Cohort 2].

The most common adverse reactions of any grade were neutropenia (71%), anaemia (45%), CRS (45%) and thrombocytopenia (43%).

The most common serious adverse reactions were CRS (12%), neutropenia (3%), bacterial infectious disorders (3%), infection with an unspecified pathogen (3%), thrombocytopenia (2%),

febrile neutropenia (2%), pyrexia (2%), aphasia (2%), headache (2%), confusional state (2%), pulmonary embolism (2%), anaemia (1%), upper gastrointestinal haemorrhage (1%) and tremor (1%).

The most common Grade 3 or higher adverse reactions included neutropenia (68%), thrombocytopenia (33%), anaemia (31%), lymphopenia (17%), leukopenia (17%), febrile neutropenia (5%) and bacterial infections (5%).

Patients who received two or more prior lines of therapy for LBCL
The adverse reactions described in this section were characterised in 384 patients infused with Breyanzi from 4 pooled studies (TRANSCEND [017001], TRANSCEND WORLD [JCAR017-BCM-001, Cohort 1, 3 and 7], PLATFORM [JCAR017-BCM-002] and OUTREACH [017007].

The most common adverse reactions of any grade were neutropenia (68%), anaemia (45%), CRS (38%), fatigue (37%) and thrombocytopenia (36%).

The most common serious adverse reactions were CRS (18%), infection with an unspecified pathogen (6%), pyrexia (4%), encephalopathy (4%), febrile neutropenia (4%), neutropenia (3%), thrombocytopenia (3%), aphasia (3%), bacterial infectious disorders (3%), tremor (3%), confusional state (3%), anaemia (2%) and hypotension (2%).

The most common Grade 3 or higher adverse reactions included neutropenia (64%), anaemia (34%), thrombocytopenia (29%), leukopenia (25%), lymphopenia (9%), infection with an unspecified pathogen (8%) and febrile neutropenia (8%).

FL

The adverse reactions described in this section were characterised in 130 patients infused with Breyanzi from study TRANSCEND-FL (FOL-001).

The most common adverse reactions of any grade were neutropenia (68%), CRS (58%), anaemia (40%), headache (29%), thrombocytopenia (29%) and constipation (21%).

The most common serious adverse reactions were CRS (9%), aphasia (4%), febrile neutropenia (3%), pyrexia (2%) and tremor (2%).

The most common Grade 3 or higher adverse reactions included neutropenia (61%), leukopenia (12%), lymphopenia (12%), thrombocytopenia (12%) and anaemia (10%).

MCL

The adverse reactions described in this section were characterised in 88 patients infused with Breyanzi from study TRANSCEND-MCL Cohort [017001].

The most common adverse reactions of any grade were CRS (61%), neutropenia (59%), anaemia (44%), fatigue (35%), thrombocytopenia (30%), and headache (23%).

The most common serious adverse reactions were CRS (24%), confusional state (6%), pyrexia (3%), mental status changes (2%), encephalopathy (2%), upper respiratory tract infection (2%), and pleural effusion (2%).

The most common Grade 3 or higher adverse reactions included neutropenia (56%), anaemia (38%), thrombocytopenia (25%), hypophosphataemia (9%), and leukopenia (7%).

Tabulated list of adverse reactions

The frequencies of adverse reactions are based on pooled data from 7 studies (TRANSCEND [017001], including LBCL and MCL Cohorts, TRANSCEND WORLD [JCAR017-BCM-001, Cohort 1, 2, 3 and 7], PLATFORM [JCAR017-BCM-002], OUTREACH [017007], TRANSFORM [BCM-003], PILOT [017006] and TRANSCEND-FL (JCAR017-FOL-001), in 779 adult patients and from post-marketing reports who received a dose of lisocabtagene maraleucel. The adverse reaction frequencies from clinical studies are based on all-cause adverse event frequencies, where a proportion of the events for an adverse reaction may have other causes.

Adverse reactions reported are presented below. These reactions are presented by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse drug reactions identified with Breyanzi

System Organ Class (SOC)	Frequency	Adverse reaction
Infections and infestations[a]	Very common	Infections - pathogen unspecified
	Common	Bacterial infectious disorders Viral infectious disorders Fungal infectious disorders
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Uncommon	Secondary malignancy of T-cell origin
Blood and lymphatic system disorders	Very common	Neutropenia Anaemia Thrombocytopenia Leukopenia Lymphopenia
	Common	Febrile neutropenia Hypofibrinogenaemia[w]
	Uncommon	Pancytopenia
Immune system disorders	Very common	Cytokine release syndrome
	Common	Hypogammaglobulinaemia[v]
	Uncommon	Haemophagocytic lymphohistiocytosis
Metabolism and nutrition disorders	Common	Hypophosphataemia
	Uncommon	Tumour lysis syndrome
Psychiatric disorders	Very common	Insomnia
	Common	Delirium[b] Anxiety

System Organ Class (SOC)	Frequency	Adverse reaction
Nervous system disorders	Very common	Headache[c] Encephalopathy[d] Dizziness[e] Tremor[f]
	Common	Aphasia[g] Peripheral neuropathy[h] Visual disturbance[i] Ataxia[j] Taste disorder[k] Cerebellar syndrome[l]
	Uncommon	Cerebrovascular disorder[m] Seizure[n] Paresis[o] Brain oedema
	Not known	Immune effector cell-associated neurotoxicity syndrome*
Cardiac disorders	Very common	Tachycardia
	Common	Arrhythmia[p]
	Uncommon	Cardiomyopathy
Vascular disorders	Very common	Hypotension
	Common	Hypertension Thrombosis[q]
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Dyspnoea[r] Pleural effusion Hypoxia
	Uncommon	Pulmonary oedema
Gastrointestinal disorders	Very common	Nausea Diarrhoea Constipation Abdominal pain Vomiting
	Common	Gastrointestinal haemorrhage[s]
Skin and subcutaneous tissue disorders	Very common	Rash
Renal and urinary disorders	Common	Acute kidney injury[t]
General disorders and administration site conditions	Very common	Fatigue Pyrexia Oedema[u]
	Common	Chills
Injury, poisoning and procedural complications	Common	Infusion related reaction

* Event was not systematically collected in clinical trials.

[a] Infections and infestations are grouped per MedDRA high level group term

[b] Delirium includes agitation, delirium, delusion, disorientation, hallucination, hallucination visual, irritability, restlessness

[c] Headache includes headache, migraine, ophthalmic migraine, sinus headache

[d] Encephalopathy includes amnesia, cognitive disorder, confusional state, depersonalisation/ derealisation disorder, depressed level of consciousness, disturbance in attention, encephalopathy, flat affect, lethargy, leukoencephalopathy, loss of consciousness, memory impairment, mental impairment, mental status changes, paranoia, somnolence, stupor

[e] Dizziness includes dizziness, dizziness postural, presyncope, syncope

[f] Tremor includes essential tremor, intention tremor, resting tremor, tremor

[g] Aphasia includes aphasia, disorganised speech, dysarthria, dysphonia, slow speech, speech disorder

[h] Peripheral neuropathy includes demyelinating polyneuropathy, hyperaesthesia, hypoaesthesia, hyporeflexia, loss of proprioception, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, sensory loss, carpal tunnel syndrome

[i] Visual disturbance includes blindness, blindness unilateral, gaze palsy, mydriasis, nystagmus, vision blurred, visual field defect, visual impairment

[j] Ataxia includes ataxia, gait disturbance

[k] Taste disorder includes dysgeusia, taste disorder
[l] Cerebellar syndrome includes balance disorder, dysdiadochokinesis, dyskinesia, dysmetria, hand-eye coordination impaired
[m] Cerebrovascular disorder includes cerebral infarction, cerebral venous sinus thrombosis, embolic cerebral infarction, haemorrhage intracranial, transient ischaemic attack
[n] Seizure includes seizure, status epilepticus
[o] Paresis includes facial paralysis, facial paresis, vocal cord paralysis
[p] Arrhythmia includes arrhythmia, atrial fibrillation, atrioventricular block complete, atrioventricular block second degree, supraventricular tachycardia, extrasystoles,ventricular extrasystoles, ventricular tachycardia
[q] Thrombosis includes deep vein thrombosis, embolism, pulmonary embolism, thrombosis, vena cava thrombosis, venous thrombosis, venous thrombosis limb
[r] Dyspnoea includes acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory failure.
[s] Gastrointestinal haemorrhage includes gastric haemorrhage, gastric ulcer haemorrhage, gastrointestinal haemorrhage, haematochezia, lower gastrointestinal haemorrhage, melaena, rectal haemorrhage, upper gastrointestinal haemorrhage
[t] Acute kidney injury includes acute kidney injury, blood creatinine increased, glomerular filtration rate decreased, renal failure, renal impairment, renal injury
[u] Oedema includes face oedema, generalised oedema, localised oedema, oedema, oedema genital, oedema peripheral, peripheral swelling, scrotal oedema, swelling, swelling face.
[v] Hypogammaglobulinemia includes blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, hypogammaglobulinaemia, immunoglobulins decreased.
[w] Hypofibrinogenaemia includes blood fibrinogen decreased, hypofibrinogenaemia

Description of selected adverse reactions

Cytokine release syndrome
For patients who received one prior line of therapy for LBCL, CRS occurred in 45% of patients, 1% of whom experienced Grade 3 CRS. The median time to onset was 4 days (range: 1 to 63 days, with the upper limit due to CRS onset, without fever, reported in one patient) and the median duration of CRS was 4 days (range: 1 to 16 days).

The most common manifestations of CRS included pyrexia (44%), hypotension (12%), chills (5%), hypoxia (5%), tachycardia (4%), headache (3%), and fatigue (2%).

In LBCL clinical studies, 42 of 177 (24%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of Breyanzi. Eighteen (10%) patients received tocilizumab only, 24 (14%) patients received tocilizumab and a corticosteroid and no patients received corticosteroids only.

For patients who received two or more prior lines of therapy for LBCL, CRS occurred in 38% of patients, 2% of whom experienced Grade 3 or 4 (severe or life-threatening) CRS. Among patients who died after receiving Breyanzi, 4 had ongoing CRS events at the time of death. The median time to onset was 4 days (range: 1 to 14 days) and the median duration was 5 days (range: 1 to 17 days).

The most common manifestations of CRS included pyrexia (38%), hypotension (18%), tachycardia (13%), chills (9%), and hypoxia (8%).

In LBCL clinical studies, 74 of 384 (19%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of Breyanzi. Thirty-seven (10%) patients received tocilizumab only, 29 (8%) received tocilizumab and a corticosteroid and 8 (2%) received corticosteroids only.

For patients who received Breyanzi for FL, CRS occurred in 58% of patients, 0.8% of whom experienced Grade 3 CRS. The median time to onset was 6 days (range: 1 to 17 days) and the median duration of CRS was 3 days (range: 1 to 10 days).

The most common manifestations of CRS included pyrexia (57%), hypotension (14%), chills (4%) hypoxia (2%) and tachycardia (0.8%).

In the FL clinical study, 33 of 130 (25%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of Breyanzi. Eighteen (14%) patients received tocilizumab only, 15 (12%) received tocilizumab and a corticosteroid and no patients received corticosteroids only. See section 4.4 for monitoring and management guidance.

For patients who received Breyanzi for MCL, CRS occurred in 61% of patients, 1% of whom experienced Grade 3 or 4 CRS. The median time to onset was 4 days (range: 1 to 10 days) and the median duration of CRS was 4 days (range: 1 to 14 days).

The most common manifestations of CRS included pyrexia (60%), hypotension (22%), hypoxia (11%) tachycardia (10%), chills (8%), headache (8%), nausea (3%), and dyspnoea (2%).

In the TRANSCEND-MCL Cohort, 24 of 88 (27%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of Breyanzi. 15 (17%) patients received tocilizumab only, 8 (9%) received tocilizumab and a corticosteroid and 1 (1%) patient received corticosteroids only.

See section 4.4 for monitoring and management guidance.

Neurologic adverse reactions
For patients who received one prior line of therapy for LBCL, CAR T-cell-associated neurologic toxicities, assessed by the investigator, occurred in 18% of patients receiving Breyanzi, including Grade 3 in 5% of patients. The median time to onset of the first event was 8 days (range: 1 to 63 days); 84% of all neurologic toxicities occurred within 2 weeks following Breyanzi infusion. The median duration of neurologic toxicities was 6 days (range: 1 to 89 days).

The most common neurologic toxicities included encephalopathy (10%), tremor (8%), aphasia (5%), dizziness (2%), and headache (1%).

For patients who received two or more prior lines of therapy for LBCL, CAR T-cell-associated neurologic toxicities assessed by the investigator occurred in 26% of patients receiving Breyanzi, including Grade 3 or 4 in 10% of patients. The median time to onset of the first event was 9 days (range: 1 to 66 days); 83% of all neurologic toxicities occurred within 2 weeks following Breyanzi infusion. The median duration of neurologic toxicities was 10 days (range: 1 to 84 days).

The most common neurologic toxicities included encephalopathy (18%), tremor (9%), aphasia (8%), delirium (7%), headache (4%), ataxia (3%) and dizziness (3%). Seizures (2%) and cerebral oedema (0.3%) have also occurred in patients treated with Breyanzi.

For patients who received Breyanzi for FL, CAR T-cell-associated neurologic toxicities, assessed by the investigator, occurred in 16% of patients receiving Breyanzi, including Grade 3 in 3% of patients. The median time to onset of the first event was 8 days (range: 4 to 16 days); 95% of all neurologic toxicities occurred within 2 weeks following Breyanzi infusion. The median duration of neurologic toxicities was 3 days (range: 1 to 17 days).

The most common neurologic toxicities included tremor (8%), aphasia (8%), encephalopathy (5%), delirium (4%) and headache (2%). See section 4.4 for monitoring and management guidance of neurologic toxicities.

For patients who received Breyanzi for MCL, CAR T-cell-associated neurologic toxicities, assessed by the investigator, occurred in 31% of patients receiving Breyanzi, including Grade 3 or 4 in 9% of patients. The median time to onset of the first event was 8 days (range: 1 to 25 days); 100% of all neurologic toxicities occurred within the first 8 weeks following Breyanzi infusion. The median duration of neurologic toxicities was 5 days (range: 1 to 45 days).

The most common neurologic toxicities included encephalopathy (26%), tremor (7%), delirium (6%), aphasia (6%), headache (5%), and dizziness (3%). Seizures (1%) have occurred in patients treated with Breyanzi.

See section 4.4 for monitoring and management guidance of neurologic toxicities.

There have been reports of fatal events of ICANS in the post-marketing setting.

Febrile neutropenia and infections
Febrile neutropenia has been observed in 7% and 9% of patients who received Breyanzi for LBCL after one prior line of therapy and two or more prior lines of therapy, respectively, in 5% of patients who received Breyanzi for FL and in 6% of patients after receiving Breyanzi for MCL.

For patients who received one prior line of therapy for LBCL, infections (all grades) occurred in 25% of patients. Grade 3 or higher infections occurred in 10% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 3% of patients, bacterial infections occurred in 5%, and viral and fungal infections occurred in 2% and none of patients, respectively.

For patients who received two or more prior lines of therapy for LBCL, infections (all grades) occurred in 38% of patients. Grade 3 or higher infections occurred in 12% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 8% of patients, bacterial infections occurred in 4% of patients, viral and fungal infections occurred in 1% of patients.

For patients who received Breyanzi for FL, infections (all grades) occurred in 20% of patients. Grade 3 occurred in 5% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 4% of patients, bacterial infections occurred in 2% of patients, viral and fungal infections occurred in 1% and none of patients, respectively.

For patients who received Breyanzi for MCL, infections (all grades) occurred in 35% of patients. Grade 3 or higher occurred in 15% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 6% of patients, bacterial infections occurred in 5% of patients, viral and fungal infections occurred in 5% and 1% of patients, respectively.

Opportunistic infections (all grades) have been observed in 2% of the 177 patients treated with Breyanzi who received one prior line of therapy for LBCL, with Grade 3 or higher opportunistic infections having occurred in 0.6% of patients. Opportunistic infections (all grades) have been observed in 3% of the 384 patients treated with Breyanzi who received two or more prior lines of therapy for LBCL, with Grade 3 or higher opportunistic infections having occurred in 1% of patients. Opportunistic infections (all grades) have been observed in 0.8% of the 130 patients treated with Breyanzi who received Breyanzi for FL, with no Grade 3 or higher opportunistic infections observed. Opportunistic infections (all grades) have been observed in 1% of the 88 patients who received Breyanzi for MCL, all of which were Grade 3 or higher.

Two fatal infections were reported from the 177 patients treated with Breyanzi who received one prior line of therapy for LBCL. Four fatal infections were reported from the 384 patients treated with Breyanzi who received two or more prior lines of therapy for LBCL among pooled LBCL studies. Of these, 1 was reported as a fatal opportunistic infection. No fatal infections were reported in the 130 patients treated with Breyanzi for FL. Two fatal infections were reported in the 88 patients treated with Breyanzi for MCL.

See section 4.4 for monitoring and management guidance.

Prolonged cytopenias
For patients who received one prior line of therapy for LBCL, Grade 3 or higher cytopenias present at Day 35 following Breyanzi administration, occurred in 35% of patients, and included thrombocytopenia (28%), neutropenia (26%), and anaemia (9%).

Of the 177 total patients treated in TRANSFORM, PILOT, and TRANSCEND WORLD (Cohort 2) who had respectively Day 35 and Day 29 laboratory findings of Grade 3-4 thrombocytopenia (n = 50) or Grade 3-4 neutropenia (n = 46) or Grade 3-4 anaemia (n = 15), for whom follow-up laboratory cytopenia results were available, the median time (min, max) to resolution (cytopenia recovering to Grade 2 or less) was as follows in days: thrombocytopenia 32 days (4, 309); neutropenia 32 days (8, 339); and anaemia 22 days (4, 64).

For patients who received two or more prior lines of therapy for LBCL, Grade 3 or higher cytopenias present at Day 29 following Breyanzi administration, occurred in 38% of patients, and included thrombocytopenia (31%), neutropenia (21%) and anaemia (7%).

Of the 384 total patients treated in TRANSCEND, TRANSCEND WORLD (Cohort 1, 3, and 7), PLATFORM, and OUTREACH who had Day 29 laboratory findings of Grade 3-4 thrombocytopenia (n = 117) or Grade 3-4 neutropenia (n = 80) or Grade 3-4 anaemia (n = 27), for whom follow-up laboratory cytopenia results were available, the median time (min, max) to resolution (cytopenia recovering to Grade 2 or less) was as follows in days: thrombocytopenia 30 days (2, 329); neutropenia 29 days (3, 337); and anaemia 15 days (3, 78).

For patients who received Breyanzi for FL, Grade 3 or higher cytopenias present at Day 29 following Breyanzi administration, occurred in 22% of patients, and included thrombocytopenia (15%), neutropenia (15%) and anaemia (5%). See section 4.4 for monitoring and management guidance.
Of the 130 total patients treated in TRANSCEND -FL who had Day 29 laboratory findings of Grade 3-4 thrombocytopenia (n = 19) or Grade 3- 4 neutropenia (n = 20) or Grade 3-4 anaemia (n = 6), for whom follow-up laboratory cytopenia results were available, the median time (min, max) to resolution (cytopenia recovering to Grade 2 or less) was as follows in days: thrombocytopenia 36 days (16, 694); neutropenia 30 days (5, 110); and anaemia 36 days (8, 64).

For patients who received Breyanzi for MCL, Grade 3 or higher cytopenias present at Day 29 following Breyanzi administration, occurred in 40% of patients, and included thrombocytopenia (32%), neutropenia (24%) and anaemia (5%).

Of the 88 total patients treated in the TRANSCEND-MCL Cohort who had Day 29 laboratory findings of Grade 3-4 thrombocytopenia (n = 28) or Grade 3-4 neutropenia (n = 21) or Grade 3-4 anaemia (n = 4), for whom follow-up laboratory cytopenia results were available, the median time (min, max) to resolution (cytopenia recovering to Grade 2 or less) was as follows in days: thrombocytopenia 30 days (5, 302); neutropenia 30 days (8, 275); and anaemia 18 days (9, 32).

See section 4.4 for monitoring and management guidance.

Hypogammaglobulinaemia
For patients who received one prior line of therapy for LBCL, adverse events of hypogammaglobulinemia occurred in 7% of patients. For patients who received two or more prior line of therapy for LBCL, adverse events of hypogammaglobulinaemia occurred in 11% of patients. For patients who received Breyanzi for FL, adverse events of hypogammaglobulinaemia occurred in 2% of patients. For patients who received Breyanzi for MCL, adverse events of hypogammaglobulinaemia occurred in 7% of patients. See section 4.4 for monitoring and management guidance.

Immunogenicity

Breyanzi has the potential to induce antibodies against this medicinal product. Humoral immunogenicity of Breyanzi was measured by determination of anti-CAR antibody pre- and post-administration. In patients who received one prior line of therapy for LBCL (TRANSFORM, PILOT and TRANSCEND WORLD, Cohort 2), pre-existing anti-therapeutic antibodies (ATAs) were detected in 0.6% (1/172) of patients, and treatment-induced ATAs were detected in 19% (32/172) of patients. In the pooled studies for patients who received two or more prior lines of therapy for LBCL (TRANSCEND and TRANSCEND WORLD, Cohort's 1 and 3), pre-existing ATAs were detected in 9% (29/309) of patients, and treatment-induced or treatment-boosted ATAs were detected in 16% (48/304) of patients. In patients who received Breyanzi for FL (TRANSCEND-FL), pre-existing anti-therapeutic antibodies (ATAs) were detected in 1.6% (2/124) of patients, and treatment-induced or treatment-boosted ATAs were detected in 26.8% (33/123) of patients. In patients who received Breyanzi for MCL (TRANSCEND-MCL Cohort), 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. The relationships between ATA status and efficacy, safety or pharmacokinetics were not conclusive due to the limited number of patients with ATAs at the study level.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No data from clinical studies are available regarding overdose of Breyanzi.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XL08

Mechanism of action

Breyanzi is a CD19-directed genetically modified autologous cellular immunotherapy administered as a defined composition to reduce variability in CD8+ and CD4+ T-cell dose. The CAR is comprised of a murine FMC63 monoclonal antibody-derived single chain variable fragment (scFv), IgG4 hinge region, CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain, and CD3 zeta activation domain. CD3 zeta signalling is critical for initiating T-cell activation and antitumour activity, while 4- 1BB (CD137) signalling enhances the expansion and persistence of Breyanzi (see section 5.2).

CAR binding to CD19 expressed on the cell surface of tumour and normal B-cells induces activation and proliferation of CAR T-cells, release of pro-inflammatory cytokines, and cytotoxic killing of target cells.

Clinical efficacy and safety

TRANSFORM
The efficacy and safety of Breyanzi was compared to the standard of care (SOC) in a phase 3, randomised, open-label, parallel group, multicentre study, TRANSFORM (BCM-003), in adult patients with large B-cell non-Hodgkin lymphoma primary refractory to or relapsed within 12 months of initial therapy, who were candidates for HSCT. The SOC consisted of salvage immunochemotherapy followed by high dose chemotherapy (HDCT) and autologous HSCT. The study included patients with diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), de novo or transformed indolent NHL, high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double/triple hit lymphoma [DHL/THL]), primary mediastinal large B-cell lymphoma (PMBCL), T-cell/histiocyte rich large B-cell lymphoma (THRBCL) or follicular lymphoma Grade 3B (FL3B), per WHO 2016 classification. The study included patients with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1, and patients with secondary CNS lymphoma involvement could be enrolled in study BCM-003 if the individual patient benefit/risk was considered positive by the investigator.

Inclusion and exclusion criteria were chosen to ensure adequate organ function, and blood counts for HSCT. The study excluded patients with a creatinine clearance of less than 45 mL/min, alanine aminotransferase (ALT) > 5 times the upper limit of normal (ULN) or left ventricular ejection fraction (LVEF) < 40%, and absolute neutrophil count (ANC) < 1.0 x 10^9 cells/L and platelets < 50 x 10^9 cells/L in absence of bone marrow involvement.

Patients were randomised 1:1 to receive either Breyanzi or SOC. Randomisation was stratified by response to first-line therapy, and secondary age adjusted international prognostic index (sAAIPI)

(0 to 1 versus 2 to 3). Patients randomised to Breyanzi were to receive lymphodepleting chemotherapy consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day concurrently for 3 days followed by Breyanzi infusion 2 to 7 days after completion of lymphodepleting chemotherapy.

In the Breyanzi arm, bridging chemotherapy was permitted between apheresis and the start of lymphodepleting chemotherapy with 1 cycle of immunochemotherapy (i.e., rituximab, dexamethasone, cytarabine, and cisplatin [R-DHAP], rituximab, ifosfamide, carboplatin, and etoposide [R-ICE], or rituximab, gemcitabine, dexamethasone, and cisplatin [R-GDP]). All patients randomised to the SOC arm were to receive 3 cycles of salvage immunochemotherapy (i.e., R-DHAP, R-ICE, or R-GDP). Patients responding (complete response [CR] and partial response [PR]) after 3 cycles were to proceed to HDCT and autologous HSCT. Patients receiving SOC treatment were allowed to receive Breyanzi if they failed to achieve CR or PR after 3 cycles of salvage immunochemotherapy, or had disease progression at any time, or if the patient needed to start a new treatment due to efficacy concerns.

Of 92 patients randomised to Breyanzi, 58 (63%) received anticancer therapy for disease control (bridging therapy), 89 (97%) received Breyanzi and 1 (1%) patient received non-conforming product. Two patients did not receive Breyanzi. Of these 2 (2%) patients, 1 (1%) did not receive Breyanzi due to manufacturing failure, and 1 (1%) patient withdrew consent prior to treatment. The median dose of Breyanzi was 99.9 x 10^6 CAR-positive viable T-cells (range: 97-103 x 10^6 CAR-positive viable T-cells).

Of 92 patients randomised to SOC, 91 (99%) patients started treatment. One (1%) patient withdrew consent before starting treatment. Forty-three (47%) patients completed immunochemotherapy, HDCT and HSCT treatment. Fifty-eight (63%) of patients went on to receive Breyanzi after failing SOC treatment.

The efficacy analyses were based on the ITT analysis set (n = 184), which was defined as all patients randomised to a treatment arm.

The median time from leukapheresis to product availability was 26 days (range: 19 to 84 days), and the median time from leukapheresis to infusion was 36 days (range: 25 to 91 days).

Table 4 summarises the baseline patient and disease characteristics in the TRANSFORM trial.

Table 4: Baseline demographic and disease-related characteristics for TRANSFORM (intention-to-treat [ITT] analysis set)

Characteristic	**Breyanzi (N = 92)**	**SOC (N = 92)**
Median age, years (range)	60.0 (20, 74)	58.0 (26, 75)
≥ 65 to < 75 years, n (%)	36 (39.1)	23 (25.0)
≥ 75 years, n (%)	0	2 (2.2)
Sex, n (%)		
Male	44 (47.8)	61 (66.3)
Female	48 (52.2)	31 (33.7)
ECOG Performance Status (at Screening)		
ECOG 0, n (%)	48 (52.2)	57 (62.0)
ECOG 1, n (%)	44 (47.8)	35 (38.0)
Disease histology subtype, n (%)		
DLBCL, NOS	53 (57.6)	50 (54.3)
DLBCL transformed from indolent lymphoma	7 (7.6)	8 (8.7)
High-grade B-cell lymphoma	22 (23.9)	21 (22.8)
PMBCL	8 (8.7)	9 (9.8)
FL3B	1 (1.1)	0
T-cell rich/histiocyte rich large B-cell lymphoma	1 (1.1)	4 (4.3)

Characteristic	Breyanzi (N = 92)	SOC (N = 92)
Chemorefractory[a], n (%)	26 (28.3)	18 (19.6)
Refractory[b], n (%)	67 (72.8)	70 (76.1)
Relapsed[c], n (%)	25 (27.2)	22 (23.9)
Confirmed CNS involvement, n (%)	1 (1.1)	3 (3.3)
Never achieved CR from prior therapies, n (%)	62 (67.4)	64 (69.6)

[a] Chemorefractory is defined as experiencing stable disease (SD) or progressive disease (PD) to last chemo-containing regimen
[b] The status was refractory if a patient achieved SD, PD, PR or CR with relapse before 3 months.
[c] The status was relapsed if a patient achieved CR with relapse on or after lasting at least 3 months but no more than 12 months.

This study demonstrated statistically significant improvements in the primary endpoint of event free survival (EFS), and key secondary endpoints of complete response (CR) rate, and progression-free survival (PFS) for patients randomised to Breyanzi compared to SOC. Efficacy was based on EFS as determined by an independent review committee (IRC) using 2014 Lugano criteria. EFS was defined as the time from randomization to death from any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization (after 3 cycles of salvage immunochemotherapy and 5 weeks after Breyanzi infusion) or start of new antineoplastic therapy due to efficacy concerns, whichever occurs first. At a pre-specified interim analysis at 80% of the information fraction with a median on-study follow up time of 6.2 months (range 0.9 to 20 months), Breyanzi demonstrated a statistically significant improvement in EFS compared to the SOC arm (HR = 0.349 [95% CI: 0.229, 0.530], one-sided p-value < 0.0001). The p-value was compared with 0.012 of the allocated alpha for the pre-specified interim analysis.

Breyanzi demonstrated an improvement compared to SOC in DLBCL (n = 60, HR: 0.357 [95% CI: 0.204, 0.625]) and HGBCL (n = 22, HR: 0.413 [95% CI: 0.189, 0.904]).

The results of the final analysis (shown in Table 5 and Figure 1), with a median on-study follow-up time of 33.86 months (range 0.9 to 53.0 months), were consistent with both the interim and primary analyses.

Table 5: TRANSFORM study: Response rate, event-free survival, progression-free survival and overall survival in patients with relapsed or refractory LBCL (ITT analysis set)

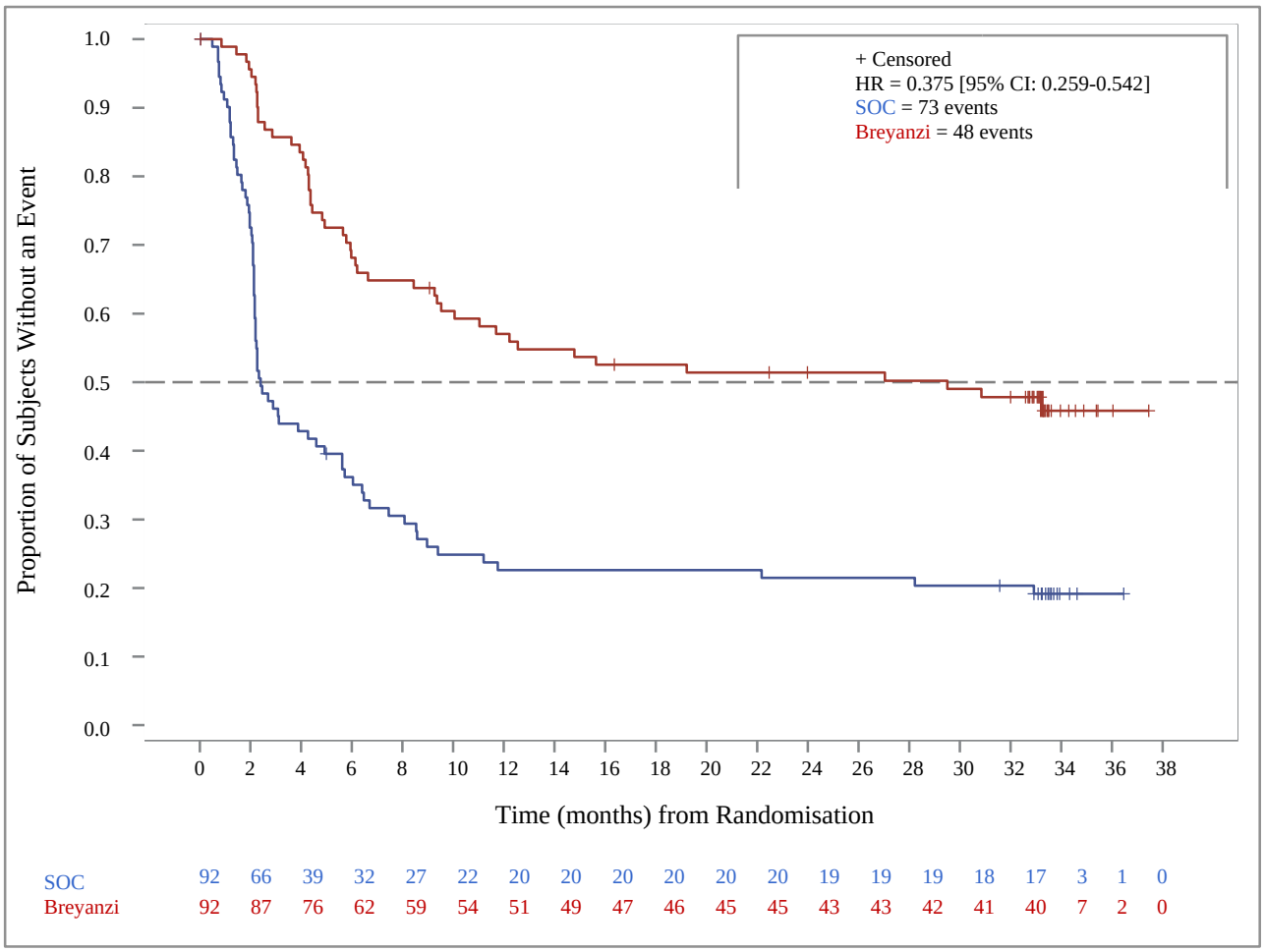
Outcome[a]	Breyanzi arm (N = 92)	SOC arm (N = 92)
Event-free survival, (months)		
Number of events n, (%)	48 (52.2)	73 (79.3)
Median [95% CI][b]	29.5 (9.5, NR)	2.4 (2.2, 4.9)
Hazard ratio [95% CI] [c]	0.375 [0.259, 0.542]	
Complete response rate		
n (%)	68 (73.9)	40 (43.5)
Two sided [95% CI]	[63.7, 82.5]	[33.2, 54.2]
Progression free survival, (months)		
Number of events n, (%)	41 (44.6)	54 (58.7)
Median [95% CI][b]	NR (12.6, NR)	6.2 (4.3, 8.6)
Hazard ratio [95% CI][c]	0.422 [0.279, 0.639]	
Overall survival (OS), (months)		
Number of events n, (%)	34 (37.0)	42 (45.7)
Median [95% CI][b]	NR (42.8, NR)	NR (18.2, NR)
Hazard ratio [95% CI][c]	0.757 [0.481, 1.191]	

NR = not reached; CI = confidence interval.

[a] Per the Lugano criteria 2014, as assessed by an IRC.
[b] Kaplan-Meier estimate.
[c] Based on a stratified Cox proportional hazards model.
[d] Greenwood's formula

Of the 92 patients in the Breyanzi arm, 80 (68 CR,12 PR) had a response with an overall response rate of 87%.

Figure 1: Kaplan-Meier plot of event-free survival based on IRC Assessment (ITT analysis set)



HR: Hazard ratio (stratified)

TRANSCEND-LBCL Cohort

The efficacy and safety of Breyanzi were evaluated in an open-label, multicentre, single-arm study, TRANSCEND (017001), in patients with relapsed or refractory (R/R) aggressive B-cell non-Hodgkin lymphoma (NHL). Eligible patients were ≥ 18 years with R/R DLBCL not otherwise specified (NOS), per WHO 2008 classification, including DLBCL arising from indolent lymphoma (transformed from follicular lymphoma, marginal zone lymphoma, chronic lymphocytic leukaemia/small lymphocytic leukaemia, Waldenström's macroglobulinaemia, or other), and high-grade B-cell lymphoma; primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), who had received at least 2 lines of therapy or after autologous haematopoietic stem cell transplant. Patients with other subtypes of DLBCL have not been included in the study and benefit-risk have not been established. The study included patients with ECOG performance status ≤ 2, prior autologous and/or allogenic haematopoietic stem cell transplant (HSCT), and secondary CNS lymphoma involvement. Patients who received prior CD19-directed therapy were eligible, provided CD19-positivity was confirmed on a tumour biopsy at any time after CD19-directed therapy. The study excluded patients with a creatinine clearance of less than 30 mL/min, alanine aminotransferase > 5 times the upper limit of normal or, left ventricular ejection fraction < 40%.

There was no minimum requirement for blood counts; patients were eligible to enroll if they were assessed by the investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy. See Table 6 for baseline demographic and disease-related characteristics.

Treatment consisted of lymphodepleting (LD) chemotherapy, fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day for 3 days, followed by Breyanzi 2 to 7 days later.

Anticancer therapy for disease control (bridging therapy) was permitted between apheresis and lymphodepletion. Of the 229 patients treated with Breyanzi, 137 (60%) received anti-cancer therapy for disease control; the type and duration of bridging therapy was left to the discretion of the investigator.

The median time from leukapheresis to product availability was 24 days (range: 17 to 51 days). In addition, the median time from leukapheresis to infusion was 38.5 days (range: 27 to 156 days).

Of 298 patients who underwent leukapheresis for whom Breyanzi was manufactured in the dose range of 44-120 x 10^6 CAR-positive viable T-cells, 229 (77%) patients received Breyanzi and 69 (23%) patients did not. Of these 69 patients, there were 27 (39%) manufacturing failures including 2 patients who did not receive Breyanzi and 25 patients who received treatment with investigational product that did not meet release specifications. Forty-two (61%) other patients were not treated with Breyanzi, the most frequent reasons being death (n = 29) or disease complications (n = 6). Among the patients treated within the range of 44-120 x 10^6 CAR-positive viable T-cells, the median dose of Breyanzi was 87 x 10^6 CAR-positive viable T-cells.

The number of patients who were evaluable for efficacy was 216 (efficacy set). Thirteen patients were not evaluable for efficacy, including 10 patients who did not have baseline positron emission tomography-positive (PET+) disease, or confirmation of PET+ disease after anticancer therapy for disease control by IRC, and 3 for other reasons.

Table 6 summarises the baseline patient and disease characteristics in the TRANSCEND study.

Table 6: Baseline demographic and disease-related characteristics for TRANSCEND

Characteristic	**All leukapheresed (N = 298)**	**Breyanzi-treated (N = 229)**
Median age, years (range)	62.0 (18, 82)	62.0 (18, 82)
≥ 65 years, n (%)	116 (38.9)	89 (38.9)
≥ 75 years, n (%)	25 (8.4)	19 (8.3)
Sex, n (%)		
Male	197 (66.1)	153 (66.8)
Female	101 (33.9)	76 (33.2)
Prior HSCT, n (%)	106 (35.6)	87 (38.0)
Autologous HSCT	100 (33.6)	84 (36.7)
Allogeneic HSCT	11 (3.7)	8 (3.5)
ECOG performance status (at screening)		
ECOG 0-1, n (%)	290 (97.3)	225 (98.3)
ECOG 2, n (%)	8 (2.7)	4 (1.7)
Disease histology subtype, n (%)		
DLBCL, NOS	142 (47.7)	117 (51.1)
DLBCL transformed from indolent lymphoma	87 (29.2)	60 (26.2)
High-grade B-cell lymphoma[a]	48 (16.1)	33 (14.4)
PMBCL	15 (5.0)	15 (6.6)
FL3B	6 (2.0)	4 (1.7)
Median number of prior therapies (range)	3 (1-12)	3 (1-8)
Chemorefractory[b], n (%)	212 (71.1)	160 (69.9)

Characteristic	All leukapheresed (N = 298)	Breyanzi-treated (N = 229)
Refractory[c], n (%)	246 (82.6)	186 (81.2)
Relapsed[d], n (%)	52 (17.4)	43 (18.8)
Secondary CNS lymphoma at time of Breyanzi infusion, n (%)	7 (2.3)	6 (2.6)
Never achieved CR from prior therapies, n (%)	141 (47.3)	103 (45.0)

[a] MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology.
[b] Chemorefractory is defined as experiencing stable disease (SD) or progressive disease (PD) to last chemo-containing regimen or relapsed < 12 months after autologous stem cell transplantation.
[c] The status was refractory if a patient achieved less than a complete response (CR) to last prior therapy.
[d] The status was relapsed if a patient achieved CR to last prior therapy.

Efficacy was assessed on the basis of the primary endpoint, overall response rate (ORR), and secondary endpoints which included CR rate, duration of response (DOR) as determined by an IRC (Table 7 and Figure 2). The median on-study follow-up time was 20.5 months (range 0.2 to 60.9 months).

Table 7: TRANSCEND study: Response rate, duration of response (IRC assessment)

	All leukapheresed (N = 298)	Efficacy set (N = 216)
Overall response rate[a], n (%)	179 (60.1)	157 (72.7)
[95% CI]	[54.3, 65.7]	[66.2, 78.5]
Complete response, n (%)	128 (43.0)	115 (53.2)
[95% CI]	[37.3, 48.8]	[46.4, 60.0]
Partial response, n (%)	51 (17.1)	42 (19.4)
[95% CI]	[13.0, 21.9]	[14.4, 25.4]
Duration of response (DOR)[a,b] (months)	n = 179	n = 157
Median	16.8	20.5
[95% CI][c]	[8.0, NR]	[8.2, NR]
Range	0.0, 34.3+	0.0, 34.3+
DOR if best response is CR[a,b] (months)	n = 128	n = 115
Median	26.1	26.1
[95% CI][c]	[23.1, NR]	[23.1, NR]
Range	0.0, 34.3+	0.0, 34.3+

CI = confidence interval; CR = complete response; IRC = Independent Review Committee; KM = Kaplan-Meier; NR = not reached
[a] Per the Lugano 2014 criteria, as assessed by IRC.
[b] Deaths after initiation of anticancer treatment were considered as events.
[c] KM method was used to obtain 2-sided 95% CI.
[+] Ongoing.

The median time to response (CR or partial response [PR]) was 1.0 months (range: 0.7 to 8.9 months). The median time to CR was 1.0 months (range: 0.8 to 12.5 months). Response durations were longer in patients who achieved a CR, as compared to patients with a best response of PR.

Six patients with secondary CNS lymphoma were treated and evaluable for efficacy in the TRANSCEND study. Three of these six patients achieved a CR; 2 of 3 patients had durable remissions of 23 months that remained ongoing at study completion. The safety profile of these patients with secondary CNS lymphoma was consistent with that observed in the overall population.

In the Efficacy set, the ORR results within PMBCL and FL3B were 79% (11/14 patients) and 100% (4/4 patients) respectively. CR rates were 50% for PMBCL and 100% for FL3B. The safety profile was consistent across these subtypes.

In the Efficacy set, the ORR results within patients with DLBCL transformed (t) from prior indolent lymphoma of FL, marginal cell lymphoma (MZL), chronic lymphocytic leukaemia/small lymphocytic

lymphoma; (CLL/SLL), and Waldenstrom macroglobulinaemia (WM) were 86% (38/44 patients), 43% (3/7 patients), 50% (2/4 patients) and 50% (1/2 patients), respectively. CR rates were 61.4% for tFL, 29% for tMZL, 25% for tCLL/SLL (Richter's syndrome), and 0% for WM, respectively. The safety profile was consistent across these subtypes. Durable remissions (i.e. DOR ≥ 12 months) were observed in patients with tFL and tMZL, however, there is very limited experience for patients with tCLL/SLL (4 patients) and tWM (2 patients) in whom maximal DORs of 2 and 5.3 months, respectively were observed. The safety profile was consistent across these subtypes.

In clinical studies of Breyanzi, 89 (39%) of the 229 patients in TRANSCEND were 65 years of age or older, and 19 (8%) were 75 years of age or older. The safety or efficacy of Breyanzi observed between these patients and younger patients was similar.

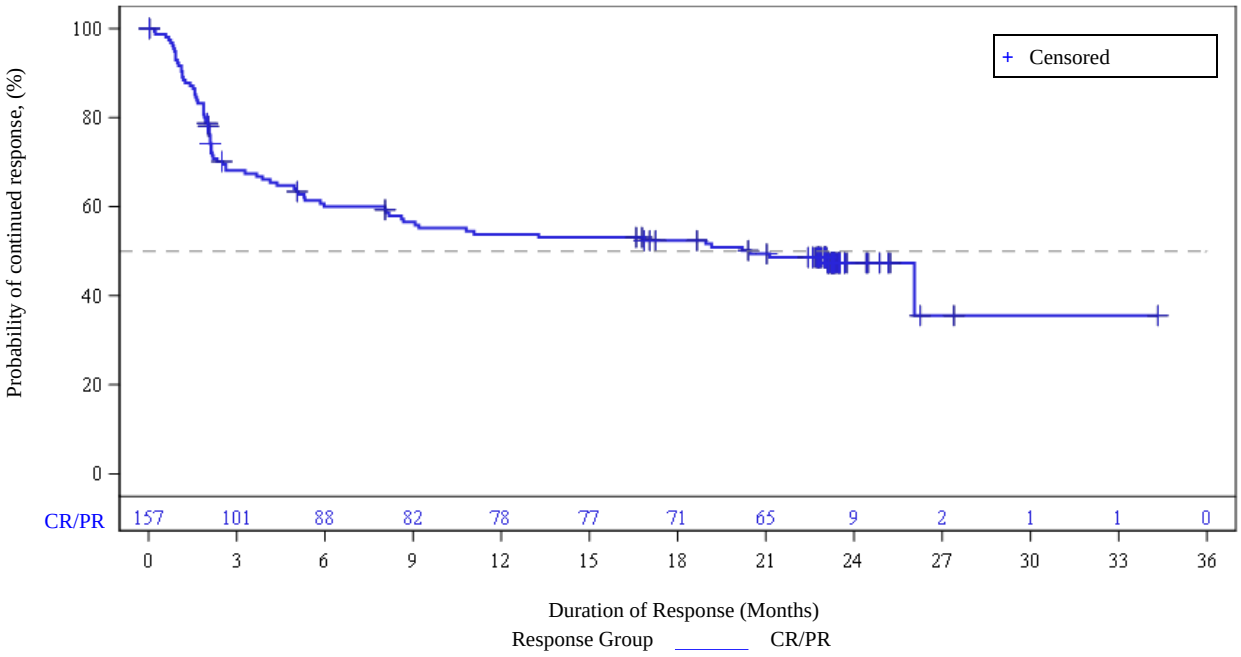
Eleven patients received prior CD19-directed therapy and had efficacy and safety outcomes similar to the overall population. All patients had CD19 expression prior to Breyanzi infusion.

There is limited experience of the use of Breyanzi for patients with ECOG performance status of 2 prior to apheresis (4 patients), and prior allogeneic HSCT (8 patients).

Amongst 229 Breyanzi-treated patients, the majority of patients (n = 209) received Breyanzi within the recommended CD4:CD8 ratio range of 0.8 to 1.2. There is limited experience of the use of Breyanzi outside this CD4:CD8 ratio range (n = 19 above 1.2, n = 1 below 0.8) which therefore limits the interpretation of the data in this subgroup.

Of the 115 patients who achieved CR, 82 (71%) had remission lasting at least 6 months and 74 (64%) had remission lasting at least 12 months.

Figure 2: Duration of response for responders per IRC assessment, TRANSCEND Efficacy set



CR = complete response; PR = partial response.
Deaths after initiation of anticancer treatment were considered as events

Eleven patients with a history of hepatitis B or hepatitis C were treated with Breyanzi without hepatitis reactivation, while receiving antiviral suppressive therapy in accordance with clinical guidelines (see section 4.4).

TRANSCEND WORLD
TRANSCEND WORLD is an ongoing single-arm, multicentre, phase 2 study. Its Cohort 1 purpose is to provide clinical experience with Breyanzi in Europe for the treatment of adult patients 3L+ large B-cell lymphoma, defined as R/R DLBCL (DLBCL NOS [de novo], transformed FL), high-grade B-cell lymphoma with MYC and BCL2 and /or BCL6 rearrangements with DLBCL histology and FL3B per WHO 2016 classification. Patients previously treated with CD19-targeted therapy were excluded. See Table 8 below for baseline demographics and disease-related characteristics.

Table 8: Baseline demographic and disease-related characteristics for TRANSCEND WORLD (Cohort 1)

Characteristic	All leukapheresed (N = 45)	Breyanzi-treated (N = 36)
Median age, years (range)	64.0 (26, 73)	61.5 (26.0, 72.0)
≥ 65 years, n (%)	19 (42.2)	14 (38.9)
≥ 75 years, n (%)	0	0
Sex, n (%)		
Male	30 (66.7)	25 (69.4)
Female	15(33.3)	11 (30.6)
Prior HSCT, n (%)	14 (31.1)	12 (33.3)
Autologous HSCT	14 (31.1)	12 (33.3)
Allogeneic HSCT	0	0
ECOG performance status (at screening)		
ECOG 0, n (%)	26 (57.8)	19 (52.8)
ECOG 1, n (%)	18 (40.0)	16 (44.4)
ECOG 2, n (%)	1 (2.2)	1 (2.8)
Disease histology subtype, n (%)		
DLBCL, NOS	36 (80.0)	31 (86.1)
High-grade B-cell lymphoma[a]	7 (15.6)	4 (11.1)
PMBCL	0	0
FL3B	2 (4.4)	1 (2.8)
Chemorefractory[b], n (%)	37 (82.2)	29 (80.6)
Refractory[c], n (%)	36 (80.0)	28 (77.8)
Relapsed[d], n (%)	9 (20.0)	8 (22.2)

[a] MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology.
[b] Chemorefractory is defined as experiencing stable disease (SD) or progressive disease (PD) to last chemo-containing regimen or relapsed < 12 months after autologous stem cell transplantation.
[c] The status was refractory if a patient achieved less than a complete response (CR) to last prior therapy.
[d] The status was relapsed if a patient achieved CR to last prior therapy.

At the time of the final analysis, 45 patients in Cohort 1 had been leukapheresed and 36 patients treated with Breyanzi, with a median follow-up time of 15.8 months. The median time from leukapheresis to product availability was 29 days (range: 24 to 38 days). In the Breyanzi-treated group, the ORR was 61.1% (95% CI: 43.5-76.9), and the CR rate was 33.3% (95% CI: 18.6-51.0). The disease burden and baseline demographics were indicative of advanced, aggressive disease characteristics. The safety profile of Breyanzi was consistent with the overall pooled safety population. See section 4.8 for adverse drug reactions associated with lisocabtagene maraleucel.

TRANSCEND-FL
The efficacy and safety of Breyanzi was evaluated in a Phase 2, open-label, multicentre, single-arm study (TRANSCEND-FL) in adult patients with relapsed or refractory FL grades 1, 2 and 3A after two or more lines of systemic therapy. The study enrolled patients with ECOG performance status of ≤ 1. The study excluded patients with a creatinine clearance of less than 30 mL/min, alanine aminotransferase > 5 times the upper limit of normal or, left ventricular ejection fraction (LVEF) ≤ 40%. There was no prespecified threshold for blood counts; patients were eligible to enroll if they

were assessed by the investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy.

Treatment consisted of lymphodepleting (LD) chemotherapy, fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day for 3 days, followed by Breyanzi 2 to 7 days later. The median dose of Breyanzi was 100 x 10^6 CAR-positive viable T-cells (range: 93.4 - 109.2 x 10^6 CAR-positive viable T-cells).

Anticancer therapy for disease control (bridging therapy) was permitted between apheresis and lymphodepletion. Of the 107 patients treated with Breyanzi, 44 (41%) received anticancer therapy, for disease control at the discretion of the investigator.

Of 114 patients who underwent leukapheresis, 107 (93.8%) patients received Breyanzi, and 4 (3.5%) patients received non-conforming product. Three (2.7%) patients did not receive Breyanzi for the following reasons: 1 (0.9%) patient due to an adverse event, 1 (0.9%) patient did not meet study criteria and 1 (0.9%) patient due to other reasons.

The number of patients who were evaluable for efficacy was 103 (efficacy set). Four patients were not evaluable for efficacy, as those patients did not have baseline PET-positive disease, or confirmation of PET-positive disease after anticancer therapy for disease control by IRC.

The median time from leukapheresis to product availability was 29 days (range: 20 to 55 days), and the median time from leukapheresis to product infusion was 50 days (range: 31 to 313 days).

Table 9: Baseline demographic and disease-related characteristics for TRANSCEND-FL

Characteristic	All leukapheresed (N = 114)	Breyanzi-treated (N = 107)
Median age, years (range)	62.0 (23, 80)	62.0 (23, 80)
≥ 65 to <75 years, n (%)	36 (31.6)	32 (29.9)
≥ 75 years, n (%)	10 (8.8)	10 (9.3)
Male gender, n (%)	72 (63.2)	66 (61.7)
Prior HSCT, n (%)		
Autologous HSCT	34 (29.8)	33 (30.8)
High FLIPI score (3-5), n (%)	66 (57.9)	61 (57.0)
Stage III-IV disease at screening, n (%)	102 (89.4)	95 (88.7)
ECOG performance status (at screening)		
ECOG 0, n (%)	68 (59.6)	65 (60.7)
ECOG 1, n (%)	46 (40.4)	42 (39.3)
Double refractory, n (%)	74 (64.9)	69 (64.5)
Progression within 24 months of first line therapy with anti-CD20 and alkylator, n (%)		
Yes	63 (55.3)	58 (54.2)
No	50 (43.9)	48 (44.9)
Not estimable	1 (0.9)	1 (0.9)
Median number of prior systemic treatments (range)	3 (2,10)	3 (2, 10)

Efficacy was based on overall response rate (ORR), defined as the percentage of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) after Breyanzi infusion as determined by an IRC (Table 10). The median on-study follow-up time was 30.0 months (range 0.3 to 39.6 months).

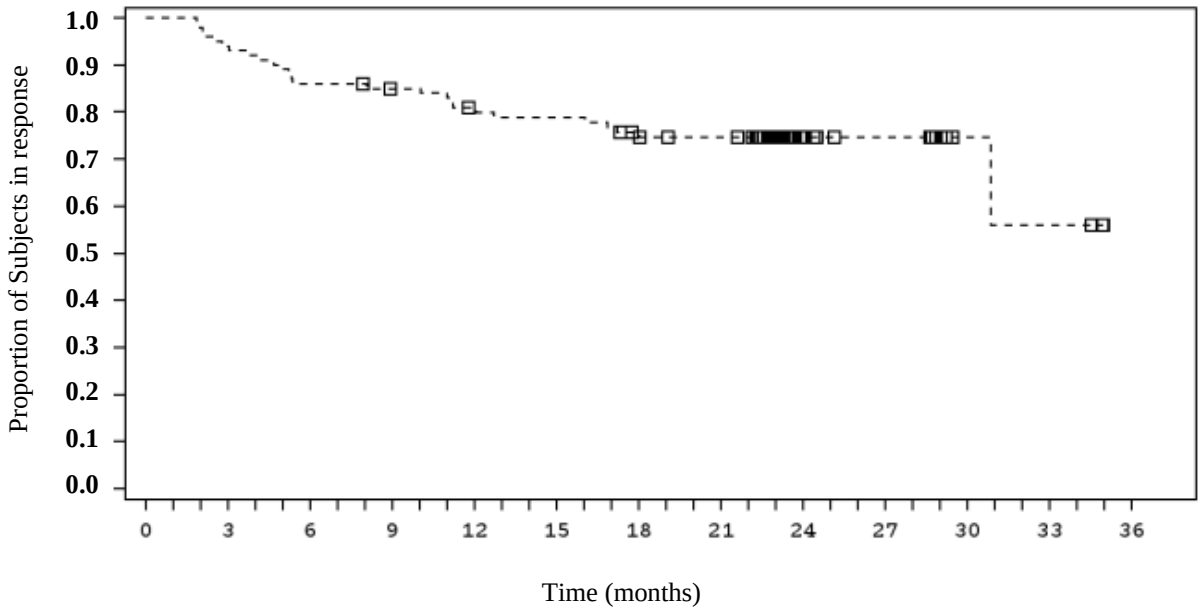
The median time to first response (CR or PR) and median time to first CR was 0.95 months (range: 0.6 to 3.3 months).

Table 10: TRANSCEND-FL study: Response rate, duration of response (IRC assessment)

	All leukapheresed (N = 114)	**Efficacy set (N = 103)**
Overall response rate[a], n (%) [95% CI][b]	106 (93.0) [86.6, 96.9]	100 (97.1) [91.7, 99.4]
Complete response, n (%) [95% CI][b]	103 (90.4) [83.4, 95.1]	97 (94.2) [87.8, 97.8]
Partial response, n (%) [95% CI][b]	3 (2.6) [0.5, 7.5]	3 (2.9) [0.6, 8.3]
Duration of response (DOR) (months)		
Median [95% CI][c]	NR [30.85, N.R]	NR [30.85, NR]
Range	1.9, 35.0+	1.9, 35.0+
Rate of continued remission[d], % [95% CI]		
At 18 months	76.1 (66.7, 83.2)	75.7 (66.0, 83.0)

CI = confidence interval; CR = complete response; NR = not reached;
+ indicates a censored value
[a] Per the Lugano 2014 criteria, as assessed by an IRC
[b] Two-sided 95% confidence interval based on exact Clopper-Pearson method.
[c] Median, Q1, Q3 are estimated from KM product-limit estimates
[d] Based on KM estimates of duration of response

Figure 3: Duration of response by IRC assessment, TRANSCEND-FL Efficacy set



Number of subjects at risk (censored)

3L +	100 (0)	94 (0)	86 (0)	83 (2)	78 (1)	76 (0)	71 (2)	68 (2)	14 (54)	10 (4)	4 (6)	3 (0)	0 (3)

TRANSCEND-MCL Cohort

The efficacy and safety of Breyanzi were evaluated in an open-label, multicenter, single-arm trial (TRANSCEND-MCL Cohort) in adult patients with relapsed or refractory MCL who had received at least 2 prior lines of therapy including a Bruton's tyrosine kinase (BTK) inhibitor, an alkylating agent, and an anti-CD20 agent. The study included patients with ECOG performance status of ≤ 2, prior autologous and/or allogeneic HSCT, and secondary CNS lymphoma involvement. The study excluded patients with a creatinine clearance ≤ 30 mL/min, alanine aminotransferase > 5 times the upper limit of normal or left ventricular ejection fraction (LVEF) < 40%. There was no prespecified threshold for

blood counts; patients were eligible to enroll if they were assessed by the investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy.

Treatment consisted of LD chemotherapy, fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day for 3 days, followed by Breyanzi 2 to 7 days later.

Anticancer therapy for disease control (bridging therapy) was permitted between apheresis and lymphodepletion. Of the 88 patients treated with Breyanzi, 58 (65.9%) received anticancer therapy for disease control, at the discretion of the investigator.

Of 104 patients who underwent leukapheresis, 88 (84.6%) patients received Breyanzi; the median dose of Breyanzi was 99.5 × 10^6 CAR-positive viable T-cells (range: 46-103 × 10^6 CAR positive viable T-cells). Four (3.8%) patients received non-conforming product. Twelve (11.5%) patients did not receive Breyanzi for the following reasons: 8 (7.6%) patients due to death, 1 (0.9%) patient no longer met eligibility criteria, and 3 (2.8%) patients due to other reasons.

Of the 88 patients who received Breyanzi, 81 patients were evaluable for efficacy and received at least 2 prior lines of systemic therapy including a BTK inhibitor, and were included in the efficacy set: five patients were not evaluable for efficacy as these patients did not have baseline PET-positive disease or confirmation of PET-positive disease after anticancer therapy for disease control by IRC, 1 patient did not receive at least 2 prior lines of systemic therapy and a BTK inhibitor and 1 patient did not receive a prior BTK inhibitor.
The median time from leukapheresis to product availability was 24.5 days (range: 17 to 80 days). In addition, the median time from leukapheresis to product infusion was 39 days (range: 28 to 489 days).

Table 11: Baseline demographic and disease-related characteristics for the TRANSCEND-MCL Cohort

Characteristic	**All leukapheresed (N = 104)**	**Breyanzi-treated (N = 88)**
Median age, years (range)	68.0 (36, 86)	68.5 (36, 86)
≥ 65, n (%)	71 (68.3)	64 (72.7)
≥ 75 years, n (%)	22 (21.2)	18 (20.5)
Sex, n (%)		
Male	81 (77.9)	67 (76.1)
Female	23 (22.1)	21 (23.9)
Prior HSCT, n (%)		
Autologous HSCT	33 (31.7)	26 (29.5)
Allogeneic HSCT	8 (7.7)	6 (6.8)
ECOG performance status (at screening)		
ECOG 0, n (%)	56 (53.8)	48 (54.5)
ECOG 1, n (%)	47 (45.2)	40 (45.5)
ECOG 2, n (%)	1 (1.0)	0
High risk features, n (%)		
Ki67 proliferation fraction ≥ 30%	82 (78.8)	66 (75.0)
TP53 mutation	25 (24.0)	20 (22.7)
Blastoid morphology	30 (28.8)	27 (30.7)
Complex Karyotype	30 (28.8)	26 (29.5)
Secondary CNS lymphoma at time of Breyanzi infusion, n (%)	7 (6.7)	7 (8.0)
Median number of prior systemic treatments (range)	3 (1, 11)	3 (1, 11)

Characteristic	All leukapheresed (N = 104)	Breyanzi-treated (N = 88)
Refractory or relapsed to last prior therapy, n (%)		
Refractory[a]	70 (67.3)	58 (65.9)
Relapsed[b]	34 (32.7)	30 (34.1)

[a] The status was refractory if a patient achieved less than a complete response (CR) to last prior therapy.
[b] The status was relapsed if a patient achieved CR to last prior therapy.

Efficacy was based on overall response rate (ORR), defined as the percentage of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) after Breyanzi infusion as determined by an IRC (Table 12). The median on-study follow-up time was 19.5 months (range 0.4 to 72 months).

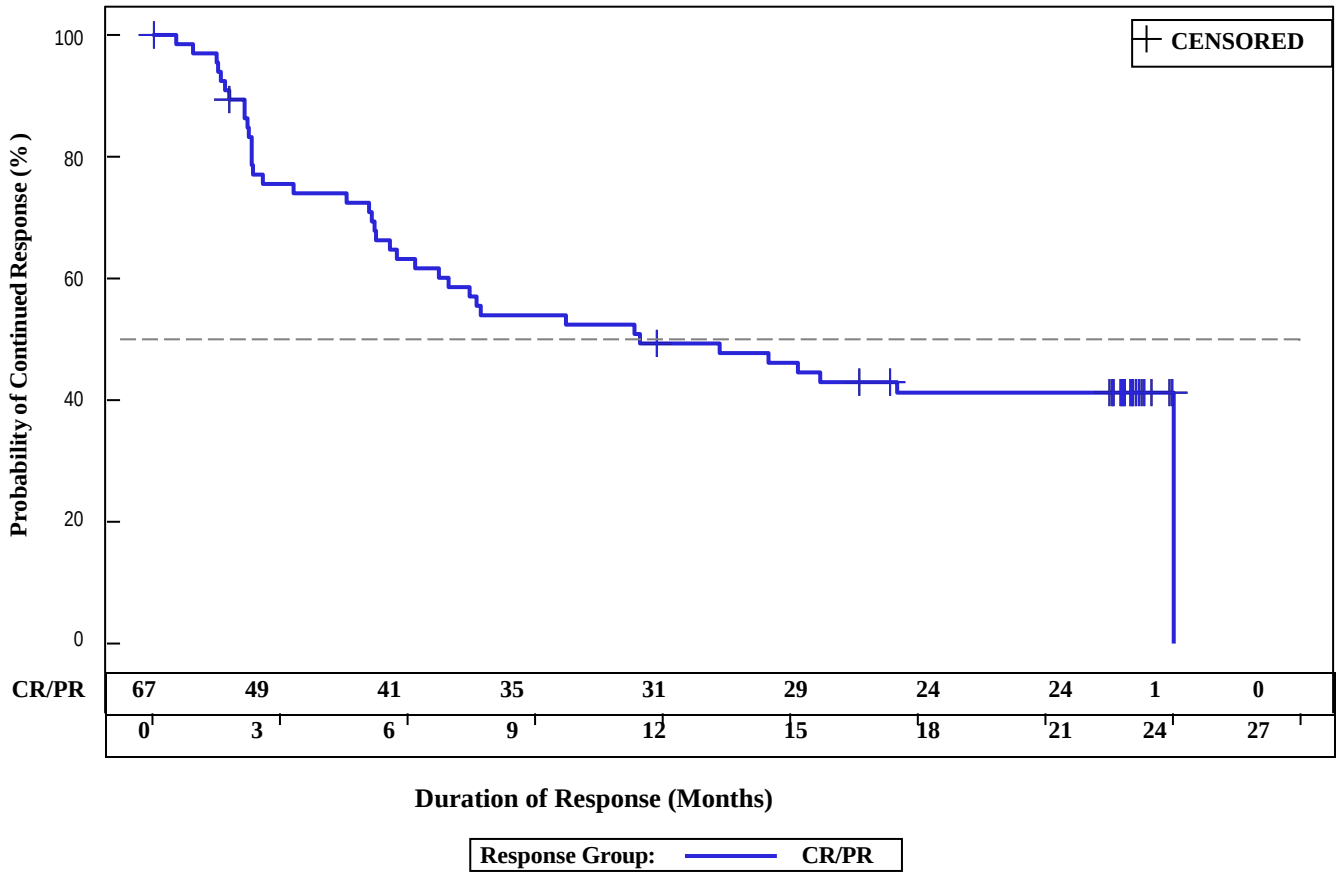
Among the 81 patients included in the efficacy set, the median time to first response (CR or PR) was 0.95 month (range: 0.7 to 3.0 months) and the median time to first CR was 0.95 month (range: 0.7 to 4.9 months). Response durations were longer in patients who achieved a BOR of CR, as compared to patients with a BOR of PR.

Table 12: TRANSCEND-MCL Cohort: Response rate, duration of response (IRC assessment)

	All Leukapheresed (N = 104)	Efficacy set (N = 81)
Overall response rate[a], n (%)	73 (70.2)	67 (82.7)
[95% CI]	[60.4, 78.8]	[72.7, 90.2]
Complete response, n (%)	64 (61.5)	58 (71.6)
[95% CI][b]	[51.5, 70.9]	[60.5, 81.1]
Partial response, n (%)	9 (8.7)	9 (11.1)
[95% CI][b]	[4.0, 15.8]	[5.2, 20.0]
Number of responders		
Duration of response (DOR) (months)		
Median [95% CI][c]	15.2 [7.0, 24.0]	11.5 [6.2, 24.0]
Range	0.0+, 24.0	0.0+, 24.0
Rate of continued remission[d], % [95% CI]		
At 24 months	44.8 (32.9; 55.9)	41.2 (29.2, 52.9)
Median follow-up for DOR (months)		
Median [95% CI]	23.0 [22,8, 23.1]	22.9 [22,8, 23.0]
Range	0.0+, 24.0	0.0+, 24.0

CI = confidence interval; CR = complete response; NR = not reached;
+ indicates a censored value
[a] Per the Lugano 2014 criteria, as assessed by an IRC
[b] Two-sided 95% confidence interval based on exact Clopper-Pearson method.
[c] Median, Q1, Q3 are estimated from KM product-limit estimates
[d] Based on KM estimates of duration of response

Figure 4 **Duration of response by IRC assessment, TRANSCEND-MCL Cohort efficacy set**



CR = complete response; PR = partial response.
PD/Death after initiation of anti-cancer treatment were considered as events

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Breyanzi in all subsets of the paediatric population in the treatment of mature B-cell neoplasms (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Following infusion, Breyanzi exhibited an initial expansion followed by a bi-exponential decline.

LBCL

In TRANSCEND-LBCL Cohort, in patients who received two or more prior lines of therapy for LBCL, the median time of maximal expansion in peripheral blood occurred 11 days after the first infusion. Breyanzi was present in peripheral blood for up to 2 years.

Among patients who received one prior line of therapy for LBCL (TRANSFORM), the median C_{max} in responders (N = 76) and non-responders (N = 7) were 33,285 and 95,618 copies/µg, respectively. The median $AUC_{0\text{-}28d}$ in responders and non-responders were 268,887 and 733,406 day*copies/ µg, respectively.

In TRANSCEND, responders (N = 150) had a 2.85-fold higher median C_{max} than non-responders (N = 45) (33,766.0 vs. 11,846.0 copies/µg). Responders had a 2.22-fold higher median $AUC_{0\text{-}28d}$ than non-responders (257,769.0 vs. 116,237.3 day*copies/µg).

In TRANSCEND, patients < 65 years old (N = 145) had a 2.93-fold and 2.35-fold higher median C_{max} and AUC_{0-28d}, respectively, compared to patients ≥ 65 years old (N = 102, including 77 patients with age 65 - 74 years, 24 with age 75 - 84 years, and 1 with age ≥ 85 years). Sex and body weight did not show clear relationships to C_{max} and AUC_{0-28d}.

FL

In TRANSCEND-FL, in patients who received two or more prior lines of therapy for FL, the median time of maximal expansion in peripheral blood occurred 10 days after the first infusion. Breyanzi was present in peripheral blood for up to 3 years.

Among patients who received Breyanzi for FL (TRANSCEND-FL), the median C_{max} in responders (N = 100) and non-responders (N = 2) were 31,336 and 15,568 copies/µg, respectively. The median AUC_{0-28d} in responders (N = 96) and non-responders (N = 2) were 245,730 and 161,935 day*copies/µg, respectively.

MCL

In the TRANSCEND-MCL Cohort, in patients who received two or more prior lines of therapy for MCL, the median time of maximal expansion in peripheral blood occurred 10 days after the first infusion. Breyanzi was present in peripheral blood for up to 2 years.

Among patients who received Breyanzi for MCL (TRANSCEND-MCL Cohort), the median C_{max} in responders (N = 67) and non-responders (N = 8) were 31,631 and 12,444 copies/µg, respectively. The median AUC_{0-28d} in responders (N = 67) and non-responders (N = 8) were 309,578 and 142,462 day*copies/µg, respectively.

5.3 Preclinical safety data

Genotoxicity assays and carcinogenicity studies were not conducted.

In vitro expansion studies from healthy donors and patients showed no evidence for transformation and/or immortalization and no preferential integration near genes of concern in Breyanzi T-cells.

Given the nature of the product, non-clinical studies on fertility, reproduction and development were not conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cryostor CS10
Sodium chloride
Sodium gluconate
Sodium acetate trihydrate
Potassium chloride
Magnesium chloride
Human albumin
N-acetyl-DL-tryptophan
Caprylic acid
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial when stored in the vapour phase of liquid nitrogen

13 months.

After thawing

The product should be administered immediately after thawing. In-use storage times and conditions should not exceed 2 hours at room temperature (15 °C-25 °C).

Do not refreeze.

6.4 Special precautions for storage

Breyanzi must be stored and transported frozen in the vapour phase of liquid nitrogen (≤ -130 °C) and must remain frozen until the patient is ready for treatment to ensure viable cells are available for patient administration. Thawed medicinal product should not be refrozen.

For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Breyanzi is supplied in cryopreservation vials made of cyclic olefin copolymer. Each 5 mL vial contains 4.6 mL cell dispersion.

The CAR-positive viable T-cells (CD8+ cell component or CD4+ cell component) are presented in individual cartons containing up to 4 vials of each component, depending upon the cryopreserved drug product CAR-positive viable T-cell concentration.

The cartons of CD8+ cell component and CD4+ cell component are contained in a single outer carton.

6.6 Special precautions for disposal and other handling

Precautions to be taken before handling or administering the medicinal product

- Breyanzi must be transported within the treatment centre in closed, break-proof, leak-proof containers.
- This medicinal product contains human blood cells. Healthcare professionals handling Breyanzi should take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.

Preparation prior to administration

Before *thawing the vials*

- Confirm the patient's identity with the patient identifiers on the shipper.
- Breyanzi is composed of CAR-positive viable T-cells formulated as separate CD8+ and CD4+ cell components; there is a separate release for infusion certificate (RfIC) for each cell component. Read the RfIC (affixed inside the shipper) for information on the number of syringes you will need and the volume to be administered of the CD8+ and CD4+ cell components (syringe labels are provided with the RfIC).

- Confirm the infusion time in advance and adjust the start time of Breyanzi thaw such that it will be available for infusion when the patient is ready.

  Note: Once the vials of CAR-positive viable T-cells (CD8+ cell and CD4+ cell components) are removed from frozen storage, the thaw must be carried to completion and the cells administered within 2 hours.

Thawing the vials

- Confirm the patient's identity with the patient identifiers on the outer carton and release for infusion certificate (RfIC).
- Remove the CD8+ cell component carton and CD4+ cell component carton from the outer carton.
- Open each inner carton and visually inspect the vial(s) for damage. If the vials are damaged, contact the company.
- Carefully remove the vials from the cartons, place vials on a protective barrier pad, and thaw at room temperature. Thaw all vials at the same time. **Take care to keep the CD8+ and CD4+ cell components separate.**

Dose preparation

- Based on the concentration of CAR-positive viable T-cells for each component, more than one vial of each of the CD8+ and CD4+ cell components may be required to complete a dose. A separate syringe should be prepared for each CD8+ or CD4+ cell component vial received.

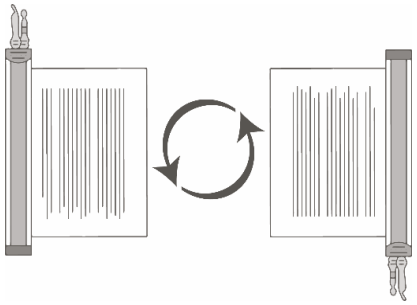
  Note: The volume to be drawn up and infused may differ for each component.

- Each 5 mL vial contains a total extractable volume of 4.6 mL of CD8+ or CD4+ cell component T-cells. The release for infusion certificate (RfIC) for each component indicates the volume (mL) of cells to be drawn up into each syringe. Use the smallest Luer-lock tip syringe necessary (1 mL to 5 mL) to draw up the specified volume from each vial. A 5 mL syringe should not be used for volumes less than 3 mL.
- **Prepare the syringe(s) of the CD8+ cell component first.** Confirm that the patient identifiers on the CD8+ cell component syringe label match the patient identifiers on the CD8+ cell component vial label. Affix the CD8+ cell component syringe labels to the syringe(s) prior to pulling the required volume into the syringe(s).
- Repeat the process for the CD4+ cell component.

  Note: It is important to confirm that the volume drawn up for each cell component matches the volume specified in the respective release for infusion certificate (RfIC).

Withdrawal of the required volume of cells from each vial into a separate syringe should be carried out using the following instructions:

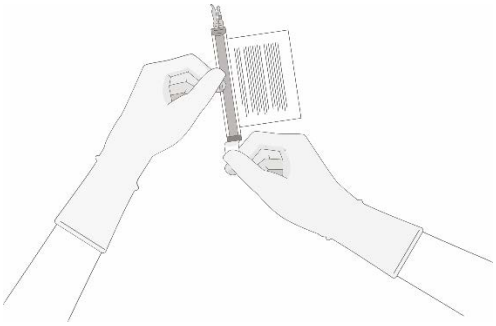
1. Hold the thawed vial(s) upright and gently invert the vial(s) to mix the cell product. If any clumping is apparent, continue to invert the vial(s) until clumps have dispersed and cells appear to be evenly resuspended.



Vial upright Vial inverted

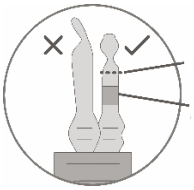
2. Visually inspect the thawed vial(s) for damage or leaks. Do not use if the vial is damaged or if the clumps do not disperse; contact the company. The liquid in the vials should be slightly opaque to opaque, colourless to yellow, or brownish-yellow.
3. Remove the polyaluminium cover (if present) from the bottom of the vial and swab the septum with an alcohol wipe. Allow to air dry before proceeding.

   NOTE: The absence of the polyaluminium cover does not impact the sterility of the vial.

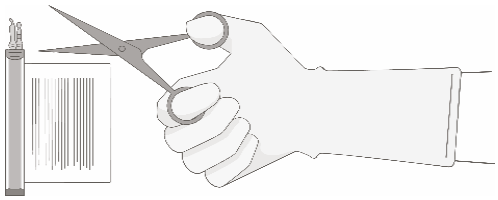


4. Keeping the vial(s) upright, cut the seal on the tubing line on the top of the vial immediately above the filter to open the air vent on the vial.

   NOTE: Be careful to select the correct tubing line with the filter. Cut ONLY the tubing <u>with</u> a filter.

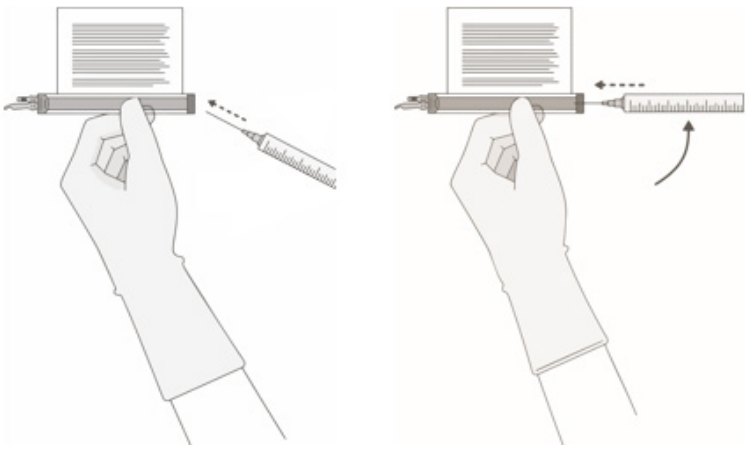


CUT HERE
Filter

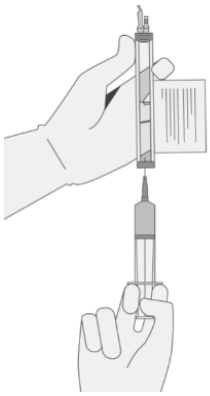


5. Hold a 20 gauge, 1-1 ½ inch needle, with the opening of the needle tip away from the retrieval port septum.
   a. Insert the needle into the septum at a 45 °-60 ° angle to puncture the retrieval port septum.
   b. Increase the angle of the needle gradually as the needle enters the vial.

a b



6. WITHOUT drawing air into the syringe, slowly withdraw the target volume (as specified in the release for infusion certificate, RfIC).

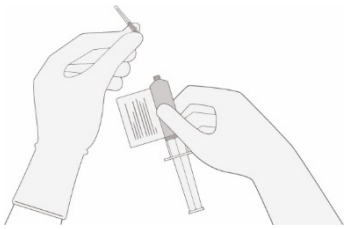


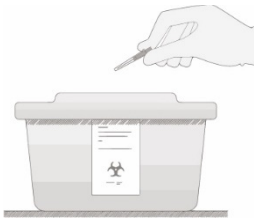
7. Carefully inspect the syringe for signs of debris prior to proceeding. If there is debris, contact the company.

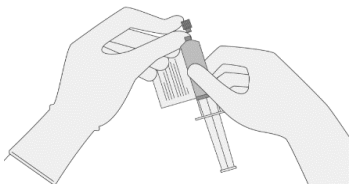
8. Verify that the volume of CD8+/CD4+ cell component matches the volume specified for the relevant component in the release for infusion certificate (RfIC).

   Once the volume is verified, shift the vial and syringe to a horizontal position, and remove the syringe/needle from the vial.

   Carefully detach the needle from the syringe and cap the syringe.







9. Continue to keep the vial horizontal and return it to the carton to avoid leaking from the vial.

10. Dispose of any unused portion of Breyanzi.

Administration

For additional information on administration, see section 4.2.

- Use intravenous sodium chloride 9 mg/mL (0.9%) solution for injection to flush all the infusion tubing prior to and after each CD8+ or CD4+ cell component administration.
- Administer the CD8+ cell component first. The entire volume of the CD8+ cell component is administered intravenously at an infusion rate of approximately 0.5 mL/minute, using the closest port or Y-arm (piggyback).
- If more than one syringe is required for a full dose of the CD8+ cell component, administer the volume in each syringe consecutively without any time between administering the contents of the syringes (unless there is a clinical reason to hold the dose, e.g., infusion reaction). After the CD8+ cell component has been administered, flush the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection.
- Administer the CD4+ cell component immediately after administration of the CD8+ cell component is complete, using the same steps and infusion rate described for the CD8+ cell component. Following administration of the CD4+ cell component, flush the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection, using enough flush to clear the tubing and the length of the IV catheter. The time for infusion will vary and will usually be less than 15 minutes for each component.

Measures to take in case of accidental exposure

- In case of accidental exposure local guidelines on handling of human derived material must be followed. Work surfaces and materials which have potentially been in contact with Breyanzi must be decontaminated with appropriate disinfectant.

Precautions to be taken for the disposal of the medicinal product

- Unused medicinal product and all material that has been in contact with Breyanzi (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1631/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 April 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substances

Juno Therapeutics Inc.
1522 217th Pl. SE
Bothell
WA 98021
United States

Celgene Corporation
556 Morris Avenue
Summit, New Jersey 07901
United States

Name and address of the manufacturer responsible for batch release

Celgene Distribution B.V.
Orteliuslaan 1000
3528 BD Utrecht
Netherlands

BMS Netherlands Operations B.V.
Francois Aragostraat 2
2342 DK Oegstgeest
Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Key elements:

Availability of tocilizumab and site qualification via the controlled distribution programme

The 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 also 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

Prior to the launch of Breyanzi in each Member State, the MAH must agree on the content and format of the educational materials with the National Competent Authority.

HCP Educational Programme
All HCPs who are expected to prescribe, dispense and administer Breyanzi shall be provided with a healthcare professional guide, which will contain information about:
- identification of CRS and serious neurologic adverse reactions 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.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
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 thirty (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 should also provide an evaluation on the need for a revision of the finished product specifications. Interim reports should be provided after approximately 15 lots and any significant out of trend results should be reported immediately.	Interim reports to be submitted in accordance with the RMP. Final report by 31 December 2026
Non-interventional post-authorisation safety study (PASS): In order to further characterise the long-term safety and efficacy of Breyanzi in its approved indications the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.	Interim reports to be submitted in accordance with the RMP. Final report: Q4-2043

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Breyanzi 1.1-70 x 10^6 cells/mL / 1.1-70 x 10^6 cells/mL dispersion for infusion
lisocabtagene maraleucel (CAR+ viable T-cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous human T-cells genetically modified with a lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR) consisting of CD8+ and CD4+ cell components with a strength of 1.1-70 x 10^6 CAR+ viable T-cells/mL for each component.

This medicine contains cells of human origin.

3. LIST OF EXCIPIENTS

Also contains: Cryostor CS10, sodium chloride, sodium gluconate, sodium acetate trihydrate, potassium chloride, magnesium chloride, human albumin, N-acetyl-DL-tryptophan, caprylic acid, water for injections. See package leaflet for further infomation.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
Contains 1-4 vials CD8+ cell component and 1-4 vials CD4+ cell component.
Contents: 4.6 mL cell dispersion/vial.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Do not irradiate.
Do NOT use a leukodepleting filter.
Read the package leaflet and release for infusion certificate before use.
STOP Confirm patient ID prior to infusion.
Give CD8+ cell component first.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only

8. EXPIRY DATE

	CD8+ cell component	CD4+ cell component
EXP		

9. SPECIAL STORAGE CONDITIONS

Store and transport frozen in the vapour phase of liquid nitrogen (≤ -130 °C).
Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells.
Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1631/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Verify patient ID
SEC:
First:
Last:
Date of birth:
JOIN:
Aph ID/DIN:

	CD8+ cell component	CD4+ cell component
Lot		

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

PARTICULARS TO APPEAR ON INNER CARTON

CARTON (CD8+ CELL COMPONENT)

1. NAME OF THE MEDICINAL PRODUCT

Breyanzi 1.1-70 x 10^6 cells/mL / 1.1-70 x 10^6 cells/mL dispersion for infusion
lisocabtagene maraleucel (CAR+ viable T-cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous human T-cells genetically modified with a lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR)
CD8+ cell component
Vial contains 5.1-322 x 10^6 CAR + viable T-cells in 4.6 mL (1.1-70 x 10^6 cells/mL).

3. LIST OF EXCIPIENTS

Also contains: Cryostor CS10, sodium chloride, sodium gluconate, sodium acetate trihydrate, potassium chloride, magnesium chloride, human albumin, N acetyl-DL-tryptophan, caprylic acid, water for injections. See outer carton and leaflet for further infomation.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
1-4 vials CAR + viable T-cells (**CD8+ cell component**).
Contents: 4.6 mL cell dispersion/vial.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Do not irradiate.
Do NOT use a leukodepleting filter.
Read the outer carton, release for infusion certificate and package leaflet before use.
1. CD8+ Give first

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport frozen in the vapour phase of liquid nitrogen (≤ -130 °C).
Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1631/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Verify patient ID
First:
Last:
Date of birth:
JOIN:
Aph ID/DIN:
Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

PARTICULARS TO APPEAR ON INNER CARTON

CARTON (CD4+ CELL COMPONENT)

1. NAME OF THE MEDICINAL PRODUCT

Breyanzi 1.1-70 x 10^6 cells/mL / 1.1-70 x 10^6 cells/mL dispersion for infusion
lisocabtagene maraleucel (CAR+ viable T-cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous human T-cells genetically modified with a lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR)
CD4+ cell component
Vial contains 5.1-322 x 10^6 CAR+ viable T-cells in 4.6 mL (1.1-70 x 10^6 cells/mL).

3. LIST OF EXCIPIENTS

Also contains: Cryostor CS10, sodium chloride, sodium gluconate, sodium acetate trihydrate, potassium chloride, magnesium chloride, human albumin, N acetyl-DL-tryptophan, caprylic acid, water for injections. See outer carton and leaflet for further infomation.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
1-4 vials CAR+ viable T-cells (**CD4+ cell component**).
Contents: 4.6 mL cell dispersion/vial.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Do not irradiate.
Do NOT use a leukodepleting filter.
Read the outer carton, release for infusion certificate and package leaflet before use.

2. CD4+ Give second

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport frozen in the vapour phase of liquid nitrogen (≤ -130 °C).
Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1631/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Verify patient ID
First:
Last:
Date of birth:
JOIN:
Aph ID/DIN:
Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL (CD8+ CELL COMPONENT)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Breyanzi 1.1-70 x 10^6 cells/mL / 1.1-70 x 10^6 cells/mL infusion
lisocabtagene maraleucel (CAR+ viable T-cells)
IV

2. METHOD OF ADMINISTRATION

1. CD8+ Give first

3. EXPIRY DATE

EXP

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Verify patient ID
First:
Last:
Date of birth:
JOIN:
Aph ID/DIN:
Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

CD8+ cell component 5.1-322 x 10^6 cells/4.6 mL

6. OTHER

For autologous use only

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL (CD4+ CELL COMPONENT)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Breyanzi 1.1-70 x 10^6 cells/mL /1.1-70 x 10^6 cells/mL infusion
lisocabtagene maraleucel (CAR+ viable T-cells)
IV

2. METHOD OF ADMINISTRATION

2. CD4+ Give second

3. EXPIRY DATE

EXP

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Verify patient ID
First:
Last:
Date of birth:
JOIN:
Aph ID/DIN:
Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

CD4+ cell component 5.1-322 x 10^6 cells/4.6 mL.

6. OTHER

For autologous use only

PARTICULARS TO APPEAR ON THE RELEASE FOR INFUSION CERTIFICATE (RfIC)

INCLUDED WITH EACH SHIPMENT FOR ONE PATIENT

1. NAME OF THE MEDICINAL PRODUCT

Breyanzi 1.1-70 x 10^6 cells/mL / 1.1-70 x 10^6 cells/mL dispersion for infusion
lisocabtagene maraleucel (CAR+ viable T-cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous human T-cells genetically modified with a lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR) consisting of CD8+ and CD4+ cell components with a strength of 1.1-70 x 10^6 CAR+ viable T-cells/mL for each component.

3. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT, AND DOSE OF THE MEDICINAL PRODUCT

Dispersion for infusion
1-4 vials CAR+ viable T-cells
Contents: 4.6 mL cell dispersion/vial.

CD8+ cell component
CD4+ cell component
Vial contains 5.1-322 x 10^6 CAR+ viable T-cells in 4.6 mL (1.1-70 x 10^6 cells/mL).

Dose of the medicinal product:
Refer to the product information for full dosing instructions.

<table>
<tr><td>Dose</td><td colspan="4">[variable field] x 10^6 CAR+ viable T-cells</td></tr>
<tr><td>CAR+ viable T-cell concentration</td><td colspan="4">[variable field] x 10^6 CAR+ viable T-cells /mL</td></tr>
<tr><td>Total volume to be dosed</td><td>[variable field] mL</td><td colspan="2">Number of vials required:</td><td>[variable field]</td></tr>
<tr><td rowspan="2">Volume to be dosed from each vial</td><td>First Vial</td><td>[variable field] mL</td><td>Third Vial</td><td>[variable field] mL or ☒ N/A</td></tr>
<tr><td>Second Vial</td><td>[variable field] mL or ☒ N/A</td><td>Fourth Vial</td><td>[variable field] mL or ☒ N/A</td></tr>
<tr><td colspan="5">Important: Use one syringe per vial. Ensure that only the listed “Volume to be dosed from each vial” is infused.</td></tr>
</table>

Syringe label(s) included in this packet

CD8+ cell component infusion volumes per syringe and syringe labels
CD4+ cell component infusion volumes per syringe and syringe labels

Note: Use one syringe per vial. Ensure that only the listed "volume to be dosed from each vial" is infused.

First Syringe volume [variable field] mL	Affix CD8+ cell component syringe #1 label here Affix CD4+ cell component syringe #1 label here Peel here
Second Syringe volume [variable field] mL OR DELETE	Affix CD8+ cell component syringe #2 label here Affix CD4+ cell component syringe #2 label here Peel here
Third Syringe volume [variable field] mL OR DELETE	Affix CD8+ cell component syringe #3 label here Affix CD4+ cell component syringe #3 label here Peel here
Fourth Syringe volume [variable field] mL OR DELETE	Affix CD8+ cell component syringe #4 label here Affix CD4+ cell component syringe #4 label here Peel here

4. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the product information before use.
Intravenous use.
Do not irradiate.
Do NOT use a leukodepleting filter.
Read the outer carton, release for infusion certificate (RfIC) and package leaflet before use.

5. OTHER SPECIAL WARNING(S), IF NECESSARY

SAVE THIS DOCUMENT AND HAVE IT AVAILABLE WHEN PREPARING FOR ADMINISTRATION OF BREYANZI

To report any concerns or if you have any questions, call:

Store a copy of this form in the patient's medical file.

For autologous use only.

6. SPECIAL STORAGE CONDITIONS

Store and transport frozen in the vapour phase of liquid nitrogen (≤ -130 °C). Do not refreeze.

7. EXPIRY DATE AND OTHER BATCH SPECIFIC INFORMATION

Product Information

Manufactured by:	
Manufacture date:	
Expiration date:	

8. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

9. BATCH NUMBER, DONATION AND PRODUCT CODES

Patient information

First name:		Last name:	
Date of birth:		Lot:	
JOIN:		Aph ID/DIN:	
SEC:			

10. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

11. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1631/001

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Breyanzi 1.1-70 x 10^6 cells/mL / 1.1-70 x 10^6 cells/mL dispersion for infusion
lisocabtagene maraleucel (chimeric antigen receptor [CAR] positive viable T-cells)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will give you a Patient card. Read it carefully and follow the instructions on it.
- Always show the Patient card to the doctor or nurse when you see them or if you go into hospital.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Breyanzi is and what it is used for

What Breyanzi is
Breyanzi contains the active substance lisocabtagene maraleucel, a type of treatment called ‘genetically modified cell therapy’.

Breyanzi is made from your own white blood cells. This involves taking some of your blood and separating out the white blood cells and sending the white blood cells to a laboratory so that they can be modified to make Breyanzi.

What Breyanzi is used for
Breyanzi is used to treat adults with a type of blood cancer called lymphoma which affects your lymph tissue and causes white blood cells to grow out of control. Breyanzi is used for:
- diffuse large B-cell lymphoma
- high-grade B-cell lymphoma
- primary mediastinal large B-cell lymphoma
- follicular lymphoma
- mantle cell lymphoma.

How Breyanzi works
- Breyanzi cells have been genetically modified to recognise the lymphoma cells in your body.
- When these cells are then introduced back into your blood, they can recognise and attack the lymphoma cells.

2. What you need to know before you are given Breyanzi

You should not be given Breyanzi:

- if you are allergic to any of the ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.
- if you cannot receive treatment, called lymphodepleting chemotherapy, which reduce the number of white blood cells in your blood (see also section 3, How Breyanzi is given).

Warnings and precautions
Before you are given Breyanzi you should tell your doctor if:

- you have any lung or heart problems
- you have low blood pressure
- you have an infection or other inflammatory conditions. The infection will be treated before you are given Breyanzi
- you have had a stem cell transplant from another person in the last 4 months – the transplanted cells can attack your body (graft-versus-host disease), causing symptoms such as rash, nausea, vomiting, diarrhoea and bloody stools
- you notice the symptoms of your cancer are getting worse. These symptoms include fever, feeling weak, night sweats, sudden weight loss
- you have had hepatitis B or C, or human immunodeficiency (HIV) infection
- you had a vaccination in the last 6 weeks or you are planning to have one in the next few months. See **Live vaccines** below for more information.

If any of the above apply to you (or you are not sure), talk to your doctor before being given Breyanzi.

Patients treated with Breyanzi may develop new types of cancers. There have been reports of patients developing cancer, beginning in a type of white blood cells called T-cells, after treatment with Breyanzi and similar medicines. Talk to your doctor if you experience any new swelling of your glands (lymph nodes) or changes in your skin such as new rashes or lumps.

Tests and checks
Before you are given Breyanzi, your doctor will:

- check your lungs, heart and blood pressure
- look for signs of infection – any infection will be treated before you receive Breyanzi
- look for signs of graft-versus-host disease, which can happen after a stem cell transplant from another person
- check your blood for uric acid and for how many cancer cells there are in your blood. This will show if you are likely to develop a condition called tumour lysis syndrome. You may be given medicines to help prevent the condition.
- check if your cancer is getting worse
- check for hepatitis B and C, and HIV infection.

After you have been given Breyanzi

- If you get certain serious side effects, you must tell your doctor or nurse straight away because you may need treatment for them. See section 4 under ‘Serious side effects’.
- Your doctor will regularly check your blood counts, as the number of blood cells may decrease.
- Stay close to the treatment centre where you had Breyanzi for at least 2 weeks. Your doctor may recommend you stay longer to make sure the care you get after your treatment meets your individual needs. See sections 3 and 4.
- Do not donate blood, organs, tissues or cells for transplantation.

You will be asked to enrol in a registry for at least 15 years in order to better understand the long-term effects of Breyanzi.

Children and adolescents
Breyanzi should not be given to children and adolescents below 18 years of age.

Other medicines and Breyanzi
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines including medicines taken without a prescription.

See section 3 for information about the medicines you will be given before having Breyanzi.

Medicines that affect your immune system
Before you are given Breyanzi tell your doctor or nurse if you are taking any medicines that weaken your immune system such as:
- corticosteroids.

This is because these medicines may reduce the effect of Breyanzi.

Other medicines that treat cancer
Some anticancer medicines could reduce the effect of Breyanzi. Your doctor will consider if you need other cancer treatments.

Live vaccines
You must not be given certain vaccines called live vaccines:
- in the 6 weeks before you are given the short course of chemotherapy (called lymphodepleting chemotherapy) to prepare your body for Breyanzi.
- during Breyanzi treatment.
- after treatment while your immune system is recovering.

Talk to your doctor if you need to have any vaccinations.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine or lymphodepleting chemotherapy. The effects of Breyanzi in pregnant or breast-feeding women are not known, and it may harm your unborn baby or breast-fed child.
- If you are pregnant or think you may be pregnant after treatment with Breyanzi, talk to your doctor immediately.
- You will be given a pregnancy test before treatment starts. Breyanzi should only be given if the result shows you are not pregnant.

Discuss the need for contraception with your doctor.

Discuss pregnancy with your doctor if you have received Breyanzi.

Driving and using machines
Do not drive, use machines, or take part in activities that need you to be alert for at least 4 weeks after treatment. Breyanzi can make you sleepy, decrease awareness, and cause confusion and seizures (fits). Based on your individual needs, your doctor may advise you to wait longer before driving.

Breyanzi contains sodium, potassium and dimethyl sulfoxide (DMSO)
This medicine contains up to 12.5 mg sodium (main component of cooking/table salt) per vial. This is equivalent to 0.6% of the recommended maximum daily intake of sodium for an adult. Up to 8 vials of this medicine may be given per dose, which in total contains 100 mg sodium or 5% of the recommended maximum daily intake of sodium for an adult.

This medicine contains up to 0.2 mmol (or 6.5 mg) potassium per dose. Your doctor will take this potassium content into consideration if your kidneys do not work properly or you are on a controlled potassium diet.

This medicine also contains DMSO which may cause severe hypersensitivity reactions.

3. How Breyanzi is given

Patient Card
- Your doctor will give you a Patient Card. Read it carefully and follow the instructions on it.
- Always show the Patient Card to the doctor or nurse when you see them or if you go to hospital.

Giving blood to make Breyanzi from your white blood cells

Breyanzi is made from your own white blood cells

- Your doctor will take some of your blood by putting a tube (catheter) in your vein. Some of your white blood cells will be separated from your blood. The rest of your blood is returned to your body. This is called leukapheresis and can take 3 to 6 hours. This process may need to be repeated.
- Your white blood cells will then be sent away to make Breyanzi.

Other medicines you will be given before Breyanzi
- A few days before you receive Breyanzi, you will be given a short course of chemotherapy. This is to clear away your existing white blood cells.
- Shortly before you receive Breyanzi, you will be given paracetamol and an antihistamine medicine. This is to reduce the risk of infusion reactions and fever.

How Breyanzi is given
- Your doctor will check that the Breyanzi was prepared from your own blood by checking that the patient identity information on the medicine labels matches your details.
- Breyanzi is given by infusion (drip) through a tube into a vein.
- You will receive infusions of the CD8 positive cells, followed immediately by infusions of the CD4 positive cells. The time for infusion will vary, but will usually be less than 15 minutes for each of the 2 cell types.

After Breyanzi is given
- Stay close to the treatment centre where you received Breyanzi – for at least 2 weeks.
- During the first week after treatment, you will need to return to the treatment centre 2 to 3 times so that your doctor can check that the treatment is working – and to help you with any side effects. See sections 2 and 4.

If you miss an appointment
Call your doctor or the treatment centre as soon as possible to make another appointment.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor immediately if you get any of the following side effects after being given Breyanzi:

- fever, chills or shaking, feeling tired, fast or uneven heartbeat, feeling light-headed and short of breath – these may be signs of a serious problem called cytokine release syndrome
- confusion, being less alert (decreased consciousness), difficulty speaking or slurred speech, shaking (tremor), feeling anxious, feeling dizzy and headache – these may be symptoms of a

condition called immune effector cell-associated neurotoxicity syndrome (ICANS), or signs of problems with your nervous system
- feeling warm, fever, chills or shivering – these may be signs of infection
  The infections may be caused by:
  - low levels of white blood cells, which help fight infections, or
  - low levels of antibodies called immunoglobulins
- blurred vision, loss of vision or double vision, difficulty speaking, weakness or clumsiness of an arm or a leg, a change in the way you walk or problems with your balance, personality changes, changes in thinking, memory and orientation leading to confusion. These may all be symptoms of a serious and potentially fatal brain condition known as progressive multifocal leukoencephalopathy (PML). These symptoms may start several months after treatment has ended and they usually develop slowly and gradually over weeks or months. It is important that your relatives or caregivers are also aware of these symptoms, since they may notice symptoms that you are not aware of.
- feeling very tired, weak and short of breath – these may be signs of low red blood cell levels (anaemia)
- bleeding or bruising more easily –these may be signs of low levels of blood cells known as platelets.

Tell your doctor immediately if you get any of the side effects above after being given Breyanzi, as you may need urgent medical treatment.

Other possible side effects

Very common: may affect more than 1 in 10 people
- difficulty sleeping
- low blood pressure including signs such as dizziness, passing out, or change in eyesight
- cough
- feeling sick or being sick
- diarrhoea or constipation
- stomach pain
- swollen ankles, arms, legs and face
- rash.

Common: may affect up to 1 in 10 people
- trouble with balancing or walking
- high blood pressure which may include signs of very bad headaches, sweating or trouble sleeping
- changes in vision
- changes in the way things taste
- numbness and tingling in the feet or hands
- blood clots or problems with blood clotting
- bleeding in your gut
- passing less urine
- infusion reactions – such as feeling dizzy, fever, and shortness of breath
- low blood levels of phosphates
- low levels of oxygen in the blood.

Uncommon: may affect up to 1 in 100 people
- a new type of cancer beginning in a type of white blood cells called T-cells (secondary malignancy of T-cell origin)
- the fast breakdown of cancer cells, resulting in the release of toxic waste products into the bloodstream – a sign may be dark urine with symptoms of nausea or pain on side of stomach
- severe inflammatory condition – symptoms may include fever, rash, enlarged liver, spleen and lymph nodes

- heart weakness, causing shortness of breath and ankle swelling
- fluid around the lungs
- stroke or mini-strokes
- convulsions or seizures (fits)
- weakness of the face muscles, vocal cords or weakness in the body
- swelling of the brain.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Breyanzi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the cartons and vial label after 'EXP'.

Store frozen in the vapour phase of liquid nitrogen (≤ -130 °C).

6. Contents of the pack and other information

What Breyanzi contains
- The active substance is lisocabtagene maraleucel. Each 4.6 mL vial contains a dispersion of CAR-positive viable T-cells (CD8 positive cell component or CD4 positive cell component) with a strength of 1.1 x 10^6 to 70 x 10^6 CAR-positive viable T-cells/mL for each cell component. There may be up to 4 vials of each of the CD8 positive or CD4 positive cell components, depending upon the concentration of cryopreserved medicine.

- The other ingredients (excipients) are Cryostor CS10 (contains dimethyl sulfoxide or DMSO), sodium chloride, sodium gluconate, sodium acetate trihydrate, potassium chloride, magnesium chloride, human albumin, N-acetyl-DL-tryptophan, caprylic acid, water for injections. See section 2, "Breyanzi contains sodium, potassium and dimethyl sulfoxide (DMSO)".

This medicine contains genetically modified human blood cells.

What Breyanzi looks like and contents of the pack
Breyanzi is a cell dispersion for infusion. It is supplied as vials of slightly opaque to opaque, colourless to yellow, or brownish-yellow dispersion. Each vial contains 4.6 mL cell dispersion of either CD8 positive or CD4 positive cell component.

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BMS Netherlands Operations B.V.
Francois Aragostraat 2
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Precautions to be taken before handling or administering the medicinal product

Breyanzi must be transported within the treatment centre in closed, break-proof, leak-proof containers.

This medicinal product contains human blood cells. Healthcare professionals handling Breyanzi should take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.

Preparation prior to administration

Before *thawing the vials*

- Confirm the patient's identity with the patient identifiers on the shipper.
- Breyanzi is composed of CAR-positive viable T-cells formulated as separate CD8+ and CD4+ cell components; there is a separate release for infusion certificate (RfIC) for each cell component. Read the RfIC (affixed inside the shipper) for information on the number of syringes you will need and the volume to be administered of the CD8+ and CD4+ cell components (syringe labels are provided with the RfIC).
- Confirm the infusion time in advance and adjust the start time of Breyanzi thaw such that it will be available for infusion when the patient is ready.

  Note: Once the vials of CAR-positive viable T-cells (CD8+ and CD4+ cell components) are removed from frozen storage, the thaw must be carried to completion and the cells administered within 2 hours.

Thawing the vials

- Confirm the patient's identity with the patient identifiers on the outer carton and the release for infusion certificate (RfIC).
- Remove the CD8+ cell component carton and CD4+ cell component carton from the outer carton.
- Open each inner carton and visually inspect the vial(s) for damage. If the vials are damaged, contact the company.
- Carefully remove the vials from the cartons, place vials on a protective barrier pad, and thaw at room temperature. Thaw all vials at the same time. **Take care to keep the CD8+ and CD4+ cell components separate.**

Dose preparation

- Based on the concentration of CAR-positive viable T-cells for each component, more than one vial of each of the CD8+ and CD4+ cell components may be required to complete a dose. A separate syringe should be prepared for each CD8+ or CD4+ cell component vial received.

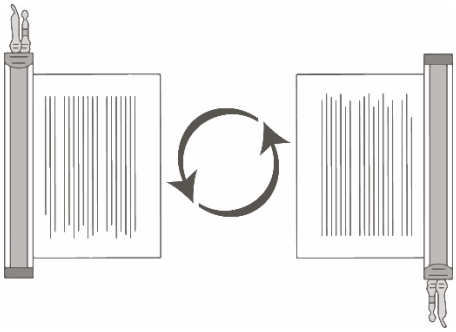
  Note: The volume to be drawn up and infused may differ for each component.

- Each 5 mL vial contains a total extractable volume of 4.6 mL of CD8+ or CD4+ cell component T-cells. The RFI Certificate for each component indicates the volume (mL) of cells to be drawn up into each syringe. Use the smallest Luer-lock tip syringe necessary (1 mL to 5 mL) to draw up the specified volume from each vial. A 5 mL syringe should not be used for volumes less than 3 mL.
- **Prepare the syringe(s) of the CD8+ cell component first.** Confirm that the patient identifiers on the CD8+ cell component syringe label match the patient identifiers on the CD8+ cell component vial label. Affix the CD8+ cell component syringe labels to the syringe(s) prior to pulling the required volume into the syringe(s).
- Repeat the process for the CD4+ cell component.

  Note: It is important to confirm that the volume drawn up for each cell component matches the volume specified in the respective release for infusion certificate (RfIC).

Withdrawal of the required volume of cells from each vial into a separate syringe should be carried out using the following instructions:

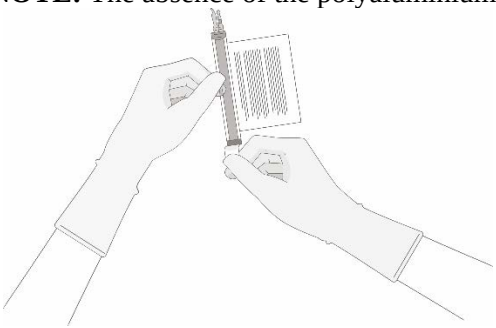
1. Hold the thawed vial(s) upright and gently invert the vial(s) to mix the cell product. If any clumping is apparent, continue to invert the vial(s) until clumps have dispersed and cells appear to be evenly resuspended.

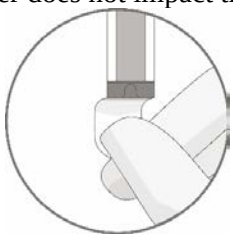


Vial upright Vial inverted

2. Visually inspect the thawed vial(s) for damage or leaks. Do not use if the vial is damaged or if the clumps do not disperse; contact the company. The liquid in the vials should be slightly opaque to opaque, colourless to yellow, or brownish-yellow.
3. Remove the polyaluminium cover (if present) from the bottom of the vial and swab the septum with an alcohol wipe. Allow to air dry before proceeding.

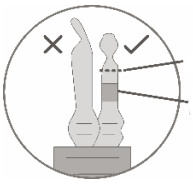
NOTE: The absence of the polyaluminium cover does not impact the sterility of the vial.



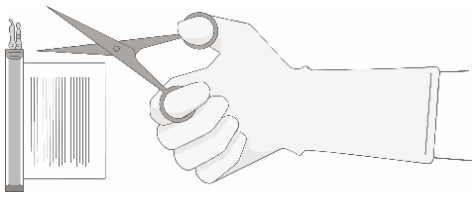


4. Keeping the vial(s) upright, cut the seal on the tubing line on the top of the vial immediately above the filter to open the air vent on the vial.

NOTE: Be careful to select the correct tubing line with the filter. Cut ONLY the tubing <u>with</u> a filter.



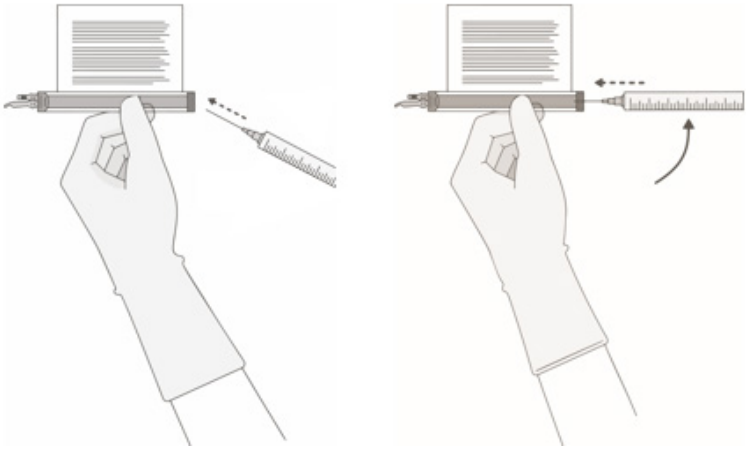
CUT HERE
Filter



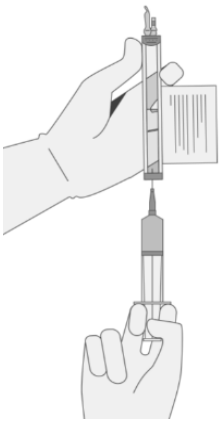
5. Hold a 20 gauge, 1-1 ½ inch needle, with the opening of the needle tip away from the retrieval port septum.

    a. Insert the needle into the septum at a 45 °-60 ° angle to puncture the retrieval port septum.
    b. Increase the angle of the needle gradually as the needle enters the vial.

a b



6. WITHOUT drawing air into the syringe, slowly withdraw the target volume (as specified in the release for infusion certificate [RfIC]).

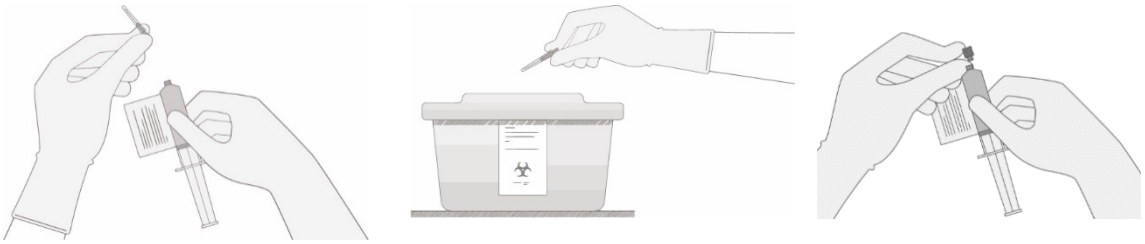


7. Carefully inspect the syringe for signs of debris prior to proceeding. If there is debris, contact the company.

8. Verify that the volume of CD8+/CD4+ cell component matches the volume specified for the relevant component in the release for infusion certificate (RfIC).

    Once the volume is verified, shift the vial and syringe to a horizontal position, and remove the syringe/needle from the vial.

    Carefully detach the needle from the syringe and cap the syringe.



9. Continue to keep the vial horizontal and return it to the carton to avoid leaking from the vial.

10. Dispose of any unused portion of Breyanzi.

Administration

- **Do NOT** use a leukodepleting filter.
- Ensure tocilizumab and emergency equipment are available prior to infusion and during the recovery period. 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 instead of tocilizumab are available on-site.
- Confirm the patient's identity matches the patient identifiers on the syringe label supplied on the respective RFI certificate.
- Once Breyanzi has been drawn into syringes, proceed with administration as soon as possible. The total time from removal of Breyanzi from frozen storage to patient administration should not exceed 2 hours.
- Use intravenous sodium chloride 9 mg/mL (0.9%) solution for injection to flush all the infusion tubing prior to and after each CD8+ or CD4+ cell component administration.
- Administer the CD8+ cell component first. The entire volume of the CD8+ cell component is administered intravenously at an infusion rate of approximately 0.5 mL/minute, using the closest port or Y-arm (piggyback).
- If more than one syringe is required for a full dose of the CD8+ cell component, administer the volume in each syringe consecutively without any time between administering the contents of the syringes (unless there is a clinical reason to hold the dose, e.g. infusion reaction). After the CD8+ cell component has been administered, flush the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection.
- Administer the CD4+ cell component immediately after administration of the CD8+ cell component is complete, using the same steps and infusion rate described for the CD8+ cell component. Following administration of the CD4+ cell component, flush the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection, using enough flush to clear the tubing and the length of the IV catheter. The time for infusion will vary and will usually be less than 15 minutes for each component.

Measures to take in case of accidental exposure

In case of accidental exposure local guidelines on handling of human derived materials must be followed. Work surfaces and materials which have potentially been in contact with Breyanzi must be decontaminated with appropriate disinfectant.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and all material that has been in contact with Breyanzi (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling human-derived material.