BREYANZI- lisocabtagene maraleucel
Juno Therapeutics, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BREYANZI safely and effectively. See full prescribing information for BREYANZI.

BREYANZI® (lisocabtagene maraleucel) suspension for intravenous infusion
Initial U.S. Approval: 2021

WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, AND SECONDARY HEMATOLOGICAL MALIGNANCIES

See full prescribing information for complete boxed warning.

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving BREYANZI. Do not administer BREYANZI to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab with or without corticosteroids (2.2, 2.3, 5.1).**
- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving BREYANZI, including concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with BREYANZI. Provide supportive care and/or corticosteroids as needed (2.2, 2.3, 5.2).**
- **T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including BREYANZI (5.8).**
- **BREYANZI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BREYANZI REMS (5.3).**

RECENT MAJOR CHANGES

Boxed Warnings	3/2024
Indications and Usage (1.2), CLL/SLL	3/2024
Dosage and Administration (2.1)	3/2024
Warnings and Precautions (5.1, 5.2, 5.5, 5.6, 5.7, 5.8, 5.10)	3/2024

INDICATIONS AND USAGE

BREYANZI is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

- adult patients with large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B, who have:
    - refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy (1.1); or
    - refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age (1.1); or
    - relapsed or refractory disease after two or more lines of systemic therapy (1.1).

Limitations of Use: BREYANZI is not indicated for the treatment of patients with primary central nervous system lymphoma (1, 14).

- adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor. This indication is approved under

accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s) (1.2).

DOSAGE AND ADMINISTRATION

For autologous use only. For intravenous use only.

- Do NOT use a leukodepleting filter (2.2).
- Administer a lymphodepleting regimen of fludarabine and cyclophosphamide before infusion of BREYANZI (2.2).
- Verify the patient's identity prior to infusion (2.2).
- Premedicate with acetaminophen and an H_1 antihistamine (2.2).
- Confirm availability of tocilizumab prior to infusion (2.2, 5.1).
- Dosing of BREYANZI is based on the number of chimeric antigen receptor (CAR)-positive viable T cells (2.1).

For LBCL:

- after one line of therapy, the dose is 90 to 110 × 10^6 CAR-positive viable T cells (2.1).
- after two or more lines of therapy, the dose is 50 to 110 × 10^6 CAR-positive viable T cells (2.1).

For CLL/SLL:

- the dose is 90 to 110 × 10^6 CAR-positive viable T cells (2.1).
- Administer BREYANZI in a REMS-certified healthcare facility (2.2, 5.1, 5.2, 5.3).

DOSAGE FORMS AND STRENGTHS

- BREYANZI is a cell suspension for infusion (3).
- A single dose of BREYANZI consists of 1:1 CAR-positive viable T cells of the CD8 and CD4 components, with each component supplied separately in one to four single-dose 5 mL vials (3). Each mL contains ≥ 1.5 × 10^6 to 70 × 10^6 CAR-positive viable T cells (3).

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Monitor for hypersensitivity reactions during infusion (5.4).
- Serious Infections: Monitor patients for signs and symptoms of infection; treat appropriately (5.5).
- Prolonged Cytopenias: Patients may exhibit Grade 3 or higher cytopenias for several weeks following BREYANZI infusion. Monitor complete blood counts (5.6).
- Hypogammaglobulinemia: Monitor and consider immunoglobulin replacement therapy (5.7).
- Secondary Malignancies: T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including BREYANZI. In the event that a secondary malignancy occurs after treatment with BREYANZI, contact Bristol-Myers Squibb at 1-888-805-4555 (5.8).
- Effects on Ability to Drive and Use Machines: Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery for at least 8 weeks after BREYANZI administration (5.9).

ADVERSE REACTIONS

The most common nonlaboratory adverse reactions (incidence ≥ 30%) in:

- LBCL are fever, cytokine release syndrome, fatigue, musculoskeletal pain, and nausea. The most common Grade 3-4 laboratory abnormalities (≥ 30%) include lymphocyte count decrease, neutrophil count decrease, platelet count decrease, and hemoglobin decrease (6.1).
- CLL/SLL are cytokine release syndrome, encephalopathy, fatigue, musculoskeletal pain, nausea, and diarrhea. The most common Grade 3-4 laboratory abnormalities (≥ 30%) include neutrophil count decrease, white blood cell decrease, hemoglobin decrease, platelet count decrease, and lymphocyte count decrease (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, AND SECONDARY HEMATOLOGICAL MALIGNANCIES

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving BREYANZI. Do not administer BREYANZI to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab with or without corticosteroids *[see Dosage and Administration (2.2, 2.3) and Warnings and Precautions (5.1)]*.**
- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving BREYANZI, including concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with BREYANZI. Provide supportive care and/or corticosteroids as needed *[see Dosage and Administration (2.2, 2.3) and Warnings and Precautions (5.2)]*.**
- **T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including BREYANZI [see Warnings and Precautions (5.8)].**
- **BREYANZI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BREYANZI REMS *[see Warnings and Precautions (5.3)]*.**

1 INDICATIONS AND USAGE

1.1 Large B-cell Lymphoma (LBCL)

BREYANZI is indicated for the treatment of adult patients with large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B who have:

- refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or
- refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or
- relapsed or refractory disease after two or more lines of systemic therapy.

Limitations of Use: BREYANZI is not indicated for the treatment of patients with primary central nervous system (CNS) lymphoma *[see Clinical Studies (14.1)].*

1.2 Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)

BREYANZI is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy including, a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor.

This indication is approved under accelerated approval based on response rate and duration of response *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

For autologous use only. For intravenous use only.

2.1 Dose

See the respective Certificate of Release for Infusion (RFI Certificate) for each component, for the actual cell counts and volumes to be infused *[see Dosage and Administration (2.2) and Dosage Forms and Strengths (3)].*

A single dose of BREYANZI contains CAR-positive viable T cells (consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components), with each component supplied separately in one to four single-dose vials. See Table 1 for dose range per indication.

Table 1: Dose Range

Indication	**BREYANZI dose range**
LBCL after two or more lines of therapy (1.1)	50 to 110 × 106 CAR-positive viable T cells
LBCL after one line of therapy (1.1)	90 to 110 × 106 CAR-positive viable T cells
CLL or SLL (1.2)	

2.2 Administration

BREYANZI is for autologous use only. The patient's identity must match the patient identifiers on the BREYANZI cartons, vials and syringe labels. Do not infuse BREYANZI if the information on the patient-specific labels does not match the intended patient.

Preparing the Patient for BREYANZI

Confirm the availability of BREYANZI before starting lymphodepleting chemotherapy.

Pretreatment

Administer the lymphodepleting chemotherapy regimen before infusion of BREYANZI: fludarabine 30 mg/m^2/day intravenously (IV), and cyclophosphamide 300 mg/m^2/day IV for 3 days. See the prescribing information for fludarabine and cyclophosphamide for

information on dose adjustment in renal impairment.

Infuse BREYANZI 2 to 7 days after completion of lymphodepleting chemotherapy.

Delay the infusion of BREYANZI if the patient has unresolved serious adverse events from preceding chemotherapies, active uncontrolled infection, or active graft-versus-host disease (GVHD).

Premedication

To minimize the risk of infusion reactions, premedicate the patient with acetaminophen (650 mg orally) and diphenhydramine (25-50 mg, IV or orally), or another H1-antihistamine, 30 to 60 minutes prior to treatment with BREYANZI.

Avoid prophylactic use of systemic corticosteroids, as they may interfere with the activity of BREYANZI.

Receipt of BREYANZI

- BREYANZI is shipped directly to the cell-associated lab or clinical pharmacy associated with the infusion center in the vapor phase of a liquid nitrogen shipper.
- Confirm the patient's identity with the patient identifiers on the shipper.
- If the patient is not expected to be ready for administration before the shipper expires and the infusion site is qualified for onsite storage, transfer BREYANZI to onsite vapor phase of liquid nitrogen storage prior to preparation.
- If the patient is not expected to be ready for administration before the shipper expires and the infusion site is not qualified for onsite storage, contact Bristol-Myers Squibb at 1-888-805-4555 to arrange for return shipment.

Preparing BREYANZI

Before *thawing the vials*

- Confirm the patient's identity with the patient identifiers on the RFI Certificate.
- Read the RFI Certificate (affixed inside the shipper) for information on the number of syringes you will need to administer the CD8 and CD4 components (syringe labels are provided with the RFI Certificate). There is a separate RFI Certificate for each cell component.
- Confirm tocilizumab and emergency equipment are available prior to infusion and during the recovery period.
- 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.

Thawing the vials

1. Confirm the patient's identity with the patient identifiers on the outer carton and on the syringe labels.
   Once the vials of CAR-positive viable T cells (CD8 component and CD4 component) are removed from frozen storage, the thaw must be carried to completion and the cells administered within 2 hours.
2. Remove the CD8 component carton and CD4 component carton from the outer carton.
3. Confirm the patient's identity with the patient identifiers on the inner carton.
4. Open each inner carton and visually inspect the vial(s) for damage. If the vials are

damaged, contact Bristol-Myers Squibb at 1-888-805-4555.

5. Confirm the patient's identity with the patient identifiers on the vials.
6. Carefully remove the vials from the cartons, place vials on a protective barrier pad, and thaw at room temperature until there is no visible ice in the vials. Thaw all of the vials at the same time.
   Keep the CD8 and CD4 components separate.

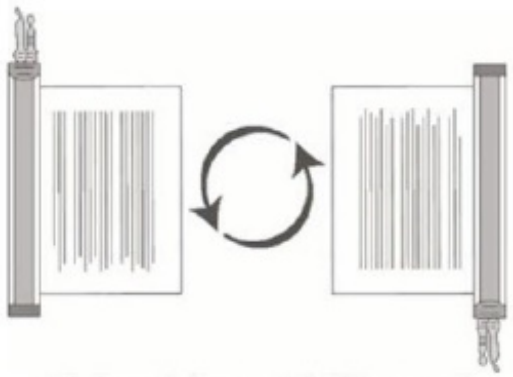
Dose preparation

- Prepare BREYANZI using sterile technique.
- Based on the concentration of CAR-positive viable T cells for each component, more than one vial of each of the CD8 and CD4 components may be required to complete a dose. A separate syringe should be prepared for each CD8 or CD4 component vial received.
  Note: The volume to be drawn up and infused may differ for each component as indicated on the RFI Certificate. Do NOT draw up excess volume into the syringe.
- Each vial contains 5 mL with a total extractable volume of 4.6 mL of CD8 or CD4 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, 3, or 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.

7. **Prepare the syringe(s) of the CD8 component first.** Affix the CD8 syringe labels to the syringe(s) prior to pulling the required volume into the syringe(s).
   Note: It is important to confirm that the volume drawn up for each component matches the volume specified in the respective RFI Certificate. Do NOT draw up excess volume into the syringe.

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

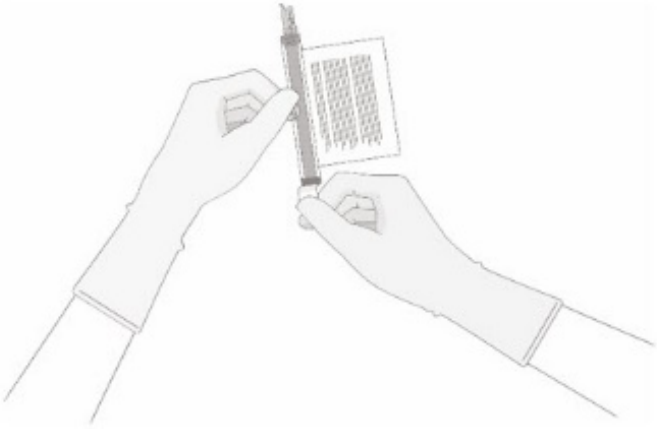
8. Hold the thawed vial(s) upright and gently invert the vial(s) 5 times to mix the cell product. If any clumping is apparent, continue to invert the vial(s) until clumps have dispersed and cells appear to be evenly resuspended.



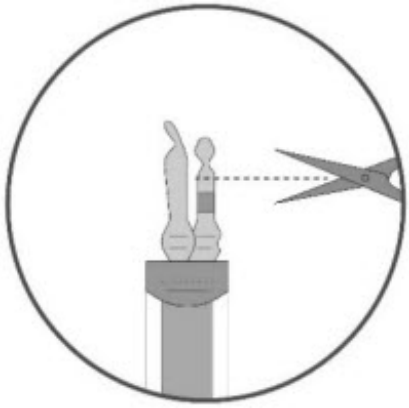
9. Visually inspect the thawed vial(s) for damage or leaks. Do not use if the vial is damaged or if the clumps do not disperse; contact Bristol-Myers Squibb at 1-888-805-4555. The liquid in the vials should be slightly opaque to opaque, colorless to

yellow or brownish-yellow.

10. Remove the polyaluminum 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 polyaluminum cover does not impact the sterility of the vial.



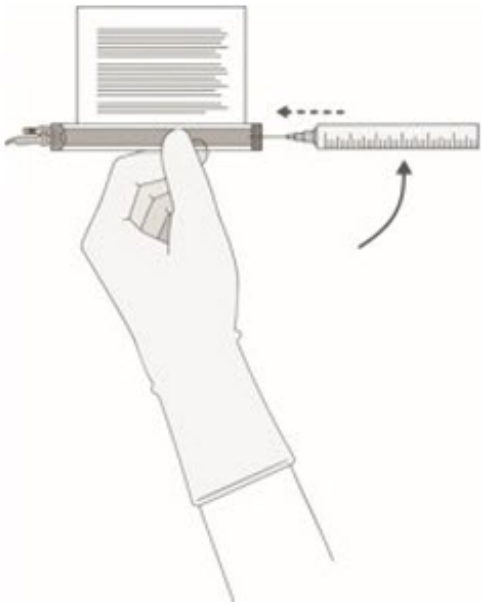
11. Keeping the vial(s) upright, cut the seal on the tubing line on the top of the vial immediately above the filter to open the air vent on the vial.
    NOTE: Be careful to select the correct tubing line with the filter. Cut ONLY the tubing <u>with</u> a filter.



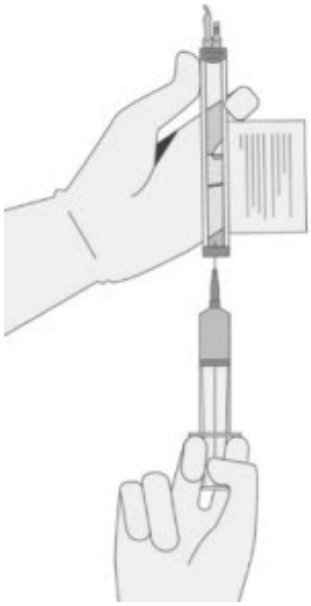
12. Hold a 20-gauge, 1-1 ½ inch needle, with the opening of the needle tip away from the retrieval port septum.

    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

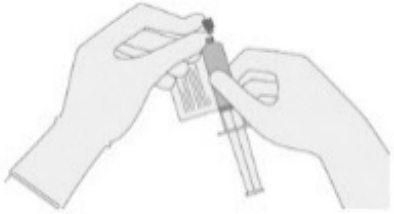


13. WITHOUT drawing air into the syringe, slowly withdraw the target volume (as specified in the RFI Certificate). Carefully inspect the syringe for signs of debris prior to proceeding. If there is debris, contact Bristol-Myers Squibb at 1-888-805-4555.



14. Verify that the volume of CD8/CD4 component matches the volume specified for the relevant component in the RFI Certificate.
    Once the volume is verified, remove the syringe/needle from the vial, carefully detach the needle from the syringe and cap the syringe.





15. Continue to keep the vial horizontal and return it to the carton to avoid leaking from the vial.
16. Dispose of any unused portion of BREYANZI (according to local biosafety guidelines).
17. Repeat the process steps 7-16 for the CD4 Component.
18. Transport the labeled CD8 and CD4 syringes to the bedside by placing with protective barrier pad inside an insulated room temperature container.

BREYANZI Administration

- **Do NOT** use a leukodepleting filter.
- Ensure tocilizumab 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.
- Once BREYANZI has 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 as indicated by the time entered on the syringe label.

1. Use intravenous normal saline to flush all the infusion tubing prior to and after each CD8 or CD4 component administration.
2. Administer the entire volume of the CD8 component intravenously at an infusion rate of approximately 0.5 mL/minute, using the closest port or Y-arm.
   NOTE: The time for infusion will vary but will usually be less than 15 minutes for each component.
3. If more than one syringe is required for a full cell dose of the CD8 component, administer the volume in each syringe consecutively without any time between administering the contents of the syringes (unless there is a clinical reason (e.g., infusion reaction) to hold the dose).
4. After the CD8 component has been administered, flush the tubing with normal saline, using enough volume to clear the tubing and the length of the IV catheter.
5. Administer the CD4 component second, immediately after administration of the CD8 component is complete, using steps 1-4, as described for the CD8 component. Following administration of the CD4 component, flush the tubing with normal saline, using enough volume to clear the tubing and the length of the IV catheter.

BREYANZI contains human blood cells that are genetically modified with replication-incompetent, self-inactivating lentiviral vector. Follow universal precautions and local biosafety guidelines applicable for the handling and disposal, to avoid potential transmission of infectious diseases.

Monitoring

- Administer BREYANZI at a REMS-certified healthcare facility.
- Monitor patients daily for at least 7 days following BREYANZI infusion at a REMS-certified healthcare facility for signs and symptoms of CRS and neurologic toxicities.
- Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.
- Instruct patients to refrain from driving or hazardous activities for at least 8 weeks following infusion.

2.3 Management of Severe Adverse Reactions

Cytokine Release Syndrome

Identify cytokine release syndrome (CRS) based on clinical presentation *[see Warnings and Precautions (5.1)]*. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 2. Patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive-care supportive therapy.

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 2 and 3
- Tocilizumab according to the CRS grade in Table 2
- Antiseizure medication according to the neurologic toxicity in Table 3

Table 2: CRS Grading and Management Guidance

CRS Grade[a]	Tocilizumab	Corticosteroids[b]
Grade 1 Fever	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. If 72 hours or more after infusion, treat symptomatically.
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% 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). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period;	If less than 72 hours after infusion, administer dexamethasone 10 mg IV every 12-24 hours. If 72 hours or more after infusion, consider dexamethasone 10 mg IV every 12-24 hours.

	maximum total of 4 doses.	
	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, maximize 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.	
Grade 3 Symptoms require and respond to aggressive intervention. 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, 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, maximize 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.	
Grade 4 Life-threatening symptoms Requirements for ventilator support or continuous veno-venous hemodialysis (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. If no improvement or continued rapid progression, maximize 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.	

[a] Lee criteria for grading CRS (Lee et al, 2014).

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

Neurologic Toxicity

Monitor patients for signs and symptoms of neurologic toxicities (Table 3). Rule out other causes of neurologic symptoms. Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities. If neurologic toxicity is suspected, manage according to the recommendations in Table 3.

If concurrent CRS is suspected during neurologic toxicity, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 2 and 3
- Tocilizumab according to the CRS grade in Table 2
- Antiseizure medication according to the neurologic toxicity in Table 3

Table 3: Neurologic Toxicity (NT) Grading and Management Guidance

NT Grade[a]	Corticosteroids and Antiseizure Medication
Grade 1	Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. If 72 hours or more after infusion, observe. If less than 72 hours after infusion, consider dexamethasone 10 mg IV every 12 to 24 hours for 2 to 3 days.
Grade 2	Start non-sedating, antiseizure 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 steroid 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 a 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	Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 10 to 20 mg IV every 8 to 12 hours. Steroids 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 edema 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.
Grade 4	Start non-sedating, antiseizure 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 edema 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.

[a] NCI CTCAE criteria for grading neurologic toxicities, version 4.03.

3 DOSAGE FORMS AND STRENGTHS

BREYANZI is a cell suspension for infusion.

A single dose of BREYANZI contains CAR-positive viable T cells that consist of CD8 and CD4 components, with each component supplied separately in single-dose vials *[see Dosage and Administration (2.1)]*.

More than one vial of each of the CD8 component and/or CD4 component may be needed to achieve the dose of BREYANZI.

Each vial contains between 6.9×10^6 and 322×10^6 CAR-positive viable T cells in 4.6 mL cell suspension (between 1.5×10^6 and 70×10^6 CAR-positive viable T cells/mL).

The infusion volume is calculated based on the concentration of cryopreserved drug product CAR-positive viable T cells. The volume may differ for each component infused. See the RFI Certificate for details *[see How Supplied/Storage and Handling (16)].*

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome

Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with BREYANZI. Among patients receiving BREYANZI for LBCL (N=418), CRS occur in 46% (190/418), including ≥ Grade 3 CRS (Lee grading system[1]) in 3.1% of patients.

In patients receiving BREYANZI after two or more lines of therapy for LBCL, CRS occurred in 46% (122/268), including ≥ Grade 3 CRS in 4.1% of patients. One patient had fatal CRS and 2 had ongoing CRS at time of death. The median time to onset was 5 days (range: 1 to 15 days). CRS resolved in 98% with a median duration of 5 days (range: 1 to 17 days).

In patients receiving BREYANZI after one line of therapy for LBCL, CRS occurred in 45% (68/150), including Grade 3 CRS in 1.3% of patients. The median time to onset was 4 days (range: 1 to 63 days). CRS resolved in all patients with a median duration of 4 days (range: 1 to 16 days).

Among patients receiving BREYANZI for CLL/SLL, CRS occurred in 83% (74/89), including Grade 3 CRS in 9% of patients. The median time to onset was 4 days (range: 1 to 18 days). CRS resolved in 97% with a median duration of 6 days (range: 2 to 37 days).

The most common manifestations of CRS (≥ 10% in LBCL or CLL/SLL) included fever (94% LBCL; 97% CLL/SLL), hypotension (42% LBCL; 46% CLL/SLL), tachycardia (28% LBCL; 8% CLL/SLL), chills (23% LBCL; 43% CLL/SLL), hypoxia (16% LBCL; 35% CLL/SLL), sinus tachycardia (22% CLL/SLL), and headache (12% LBCL; 18% CLL/SLL) *[see Adverse Reactions (6.1)].*

Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, diffuse alveolar damage, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) *[see Adverse Reactions (6.1)].*

Ensure that 2 doses of tocilizumab are available prior to infusion of BREYANZI.

Of the patients who received BREYANZI for LBCL (n=418) and CLL/SLL (n=89), 23% (LBCL) and 64% (CLL/SLL) received tocilizumab and/or a corticosteroid for CRS, including 10% (LBCL) and 33% (CLL/SLL) who received tocilizumab only and

2.2% (LBCL) and 2.2% (CLL/SLL) who received corticosteroids only.

Monitor patients daily for at least 7 days following BREYANZI infusion at a REMS-certified healthcare facility for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for at least 4 weeks after infusion. At the first sign of CRS, institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids as indicated *[see Dosage and Administration (2.3)]*.

Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time *[see Patient Counseling Information (17)].*

5.2 Neurologic Toxicities

Neurologic toxicities that were fatal or life-threatening, including immune effector cell-associated neurotoxicity syndrome (ICANS), occurred following treatment with BREYANZI. Serious events including cerebral edema and seizures occurred with BREYANZI. Fatal and serious cases of leukoencephalopathy, some attributable to fludarabine, also occurred.

In patients receiving BREYANZI after two or more lines of therapy for LBCL, CAR T cell-associated neurologic toxicities occurred in 35% (95/268), including ≥ Grade 3 cases in 12% of patients. Three patients had fatal neurologic toxicity and 7 had ongoing neurologic toxicity at time of death. The median time to onset of neurotoxicity was 8 days (range: 1 to 46 days). Neurologic toxicities resolved in 85% of patients with a median duration of 12 days (range: 1 to 87 days).

In patients receiving BREYANZI after one line of therapy for LBCL, CAR T cell-associated neurologic toxicities occurred in 27% (41/150) of patients, including Grade 3 cases in 7% of patients. The median time to onset of neurologic toxicity was 8 days (range: 1 to 63 days). The median duration of neurologic toxicity was 6 days (range: 1 to 119 days).

In all patients combined receiving BREYANZI for LBCL, CAR T cell-associated neurologic toxicities occurred in 33% (136/418), including ≥ Grade 3 cases in 10% of patients. The median time to onset was 8 days (range: 1 to 63), with 87% of cases developing by 16 days. Neurologic toxicities resolved in 85% of patients with a median duration of 11 days (range: 1 to 119 days). Of patients developing neurotoxicity, 77% (105/136) also developed CRS.

In patients receiving BREYANZI for CLL/SLL, CAR T cell-associated neurologic toxicities occurred in 46% (41/89), including Grade 3 cases in 20% of patients and a single Grade 4 case. The median time to onset of neurotoxicity was 7 days (range: 1 to 21 days), with 95% of cases developing by 16 days. Neurologic toxicities resolved in 85% with a median duration of 7 days (range: 1 to 83 days). Of patients developing neurotoxicity, 95% (39/41) also developed CRS.

The most common neurologic toxicities (≥ 5% in LBCL or CLL) included encephalopathy (20% LBCL; 36% CLL/SLL), tremor (13% LBCL; 14% CLL/SLL), aphasia (8% LBCL; 8% CLL/SLL), headache (6% LBCL; 9% CLL/SLL), dizziness (6% LBCL), and delirium (5% LBCL; 12% CLL/SLL).

Monitor patients daily for at least 7 days following BREYANZI infusion at a REMS-certified healthcare facility for signs and symptoms of neurologic toxicities and assess for other causes of neurological symptoms. Monitor patients for signs or symptoms of neurologic toxicities for at least 4 weeks after infusion and treat promptly. Manage neurologic

toxicity with supportive care and/or corticosteroid as needed *[see Dosage and Administration (2.3)]*.

Counsel patients to seek immediate medical attention should signs or symptoms of neurologic toxicity occur at any time *[see Patient Counseling Information (17)]*.

5.3 BREYANZI REMS

Because of the risk of CRS and neurologic toxicities, BREYANZI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BREYANZI REMS *[see Boxed Warning and Warnings and Precautions (5.1, 5.2)]*. The required components of the BREYANZI REMS are:

- Healthcare facilities that dispense and administer BREYANZI must be enrolled and comply with the REMS requirements.
- Certified healthcare facilities must have on-site, immediate access to tocilizumab.
- Ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after BREYANZI infusion, if needed for treatment of CRS.

Further information is available at www.BreyanziREMS.com, or contact Bristol-Myers Squibb at 1-866-340-7332.

5.4 Hypersensitivity Reactions

Allergic reactions may occur with the infusion of BREYANZI. Serious hypersensitivity reactions, including anaphylaxis, may be due to dimethyl sulfoxide (DMSO).

5.5 Serious Infections

Severe infections, including life-threatening or fatal infections, have occurred in patients after BREYANZI infusion.

In patients receiving BREYANZI, infections of any grade occurred in 36% (LBCL) and 35% (CLL/SLL), with Grade 3 or higher infections occurred in 12% (LBCL) and 16% (CLL/SLL) of all patients. Grade 3 or higher infections with an unspecified pathogen occurred in 7% (LBCL) and 10% (CLL/SLL), bacterial infections in 4.3% (LBCL) and 2.2% (CLL/SLL), viral infections in 1.9% (LBCL) and 1.1% (CLL/SLL), and fungal infections in 0.5% (LBCL) and 2.2% (CLL/SLL).

Febrile neutropenia developed after BREYANZI infusion in 8% (LBCL) and 12% (CLL/SLL) of patients. Febrile neutropenia may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids, and other supportive care as medically indicated.

Monitor patients for signs and symptoms of infection before and after BREYANZI administration and treat appropriately. Administer prophylactic antimicrobials according to standard institutional guidelines.

Avoid administration of BREYANZI in patients with clinically significant, active systemic infections.

Viral Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against B

cells.

In patients who received BREYANZI, 15 of 16 LBCL patients, and all 9 CLL/SLL patients with a prior history of HBV were treated with concurrent antiviral suppressive therapy. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing. In patients with prior history of HBV, consider concurrent antiviral suppressive therapy to prevent HBV reactivation per standard guidelines.

5.6 Prolonged Cytopenias

Patients may exhibit cytopenias not resolved for several weeks following lymphodepleting chemotherapy and BREYANZI infusion.

Grade 3 or higher cytopenias persisted at Day 29 following BREYANZI infusion in 36% (LBCL) and 45% (CLL/SLL) of patients, and included thrombocytopenia in 28% (LBCL) and 23% (CLL/SLL), neutropenia in 21% (LBCL) and 35% (CLL/SLL), and anemia in 6% (LBCL) and 12% (CLL/SLL).

Monitor complete blood counts prior to and after BREYANZI administration.

5.7 Hypogammaglobulinemia

B-cell aplasia and hypogammaglobulinemia can occur in patients receiving BREYANZI.

In patients receiving BREYANZI, hypogammaglobulinemia was reported as an adverse reaction in 11% (LBCL) and 14% (CLL/SLL) of patients. Hypogammaglobulinemia, either as an adverse reaction or laboratory IgG level below 500 mg/dL after infusion, was reported in 28% (LBCL) and 37% (CLL/SLL) of patients.

Monitor immunoglobulin levels after treatment with BREYANZI and manage using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement as clinically indicated.

Live Vaccines

The safety of immunization with live viral vaccines during or following BREYANZI treatment has not been studied. Vaccination with live virus 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 with BREYANZI.

5.8 Secondary Malignancies

Patients treated with BREYANZI may develop secondary malignancies. T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including BREYANZI. Mature T cell malignancies, including CAR-positive tumors, may present as soon as weeks following infusion, and may include fatal outcomes *[see Boxed Warning, Adverse Reactions (6.3), Patient Counseling Information (17)]*.Monitor lifelong for secondary malignancies. In the event that a secondary malignancy occurs, contact Bristol-Myers Squibb at 1-888-805-4555 for reporting and to obtain instructions on collection of patient samples for testing.

5.9 Effects on Ability to Drive and Use Machines

Due to the potential for neurologic events, including altered mental status or seizures, patients receiving BREYANZI are at risk for developing altered or decreased consciousness or impaired coordination in the 8 weeks following BREYANZI administration. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks.

5.10 Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome (IEC-HS)

Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome (IEC-HS), including fatal or life-threatening reactions, occurred following treatment with BREYANZI. Three of 89 (3%) safety evaluable patients with R/R CLL/SLL developed IEC-HS. Time to onset of IEC-HS ranged from 7 to 18 days. Two of the 3 patients developed IEC-HS in the setting of ongoing CRS and 1 in the setting of ongoing neurotoxicity. IEC-HS was fatal in 2 of 3 patients. One patient had fatal IEC-HS and one had ongoing IEC-HS at time of death.

IEC-HS is a life-threatening condition with a high mortality rate if not recognized and treated early. Treatment of IEC-HS should be administered per current practice guidelines.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Cytokine Release Syndrome *[see Warnings and Precautions (5.1, 5.3)]*
- Neurologic Toxicities *[see Warnings and Precautions (5.2, 5.3)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.4)]*
- Serious Infections *[see Warnings and Precautions (5.5)]*
- Prolonged Cytopenias *[see Warnings and Precautions (5.6)]*
- Hypogammaglobulinemia *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described in the WARNINGS and PRECAUTIONS and in this section reflect exposure to a single dose of BREYANZI in one randomized, open-label study with 89 patients (TRANSFORM) with relapsed or refractory LBCL, and three open-label, single-arm studies with 61 patients (PILOT) and 268 patients (TRANSCEND) with relapsed or refractory LBCL, and 89 patients with relapsed or refractory CLL/SLL (TRANSCEND-CLL).

Relapsed or Refractory LBCL After One Line of Therapy

TRANSFORM

The safety of BREYANZI was evaluated in the TRANSFORM, a randomized, open-label, multicenter study, in which patients with primary refractory LBCL or relapse within 1 year of first-line chemoimmunotherapy received BREYANZI (N=89) or standard therapy (N=91) *[see Clinical Studies (14.1)].* Patients had not yet received treatment for relapsed

or refractory lymphoma and were potential candidates for autologous HSCT. The trial excluded patients who were ineligible for transplant or who had age > 75 years, ECOG performance status >1, history of central nervous system (CNS) disorders (such as seizures or cerebrovascular ischemia), uncontrolled infection, CrCl < 45 mL/min, ALT > 5 times the upper limit of normal (ULN), LVEF < 40%, or absolute neutrophil count (ANC) < 1.0×10^9 cells/L or platelets < 50×10^9 cells/L in the absence of bone marrow involvement.

The planned dose of BREYANZI was 100×10^6 CAR-positive viable T cells. The median age of the BREYANZI-treated population was 59 years (range: 20 to 74 years); 47% were male; 58% were white, 11% were Asian, and 5% were black.

Serious adverse reactions occurred in 38% of patients. The most common nonlaboratory, serious adverse reactions (> 2%) were CRS, sepsis, fever, febrile neutropenia, headache, aphasia, COVID-19 infection, and pulmonary embolism.

Table 4 presents selected nonlaboratory adverse reactions in patients treated with BREYANZI, and Table 5 describes selected new or worsening Grade 3 or 4 laboratory abnormalities.

The most common nonlaboratory adverse reactions (≥ 20%) were fever, CRS, musculoskeletal pain, headache, fatigue, nausea, constipation, and dizziness.

Table 4: Adverse Reactions in ≥ 10% of Patients Treated with BREYANZI in the TRANSFORM Study (N=89)

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
Blood and lymphatic system disorders		
Febrile neutropenia	10	10
Cardiac disorders		
Tachycardia[a]	15	1.1
Gastrointestinal disorders		
Nausea	24	0
Constipation	20	2.2
Diarrhea	18	0
Abdominal pain[b]	13	2.2
Vomiting	11	0
General disorders and administration site conditions		
Fever	55	3.4
Fatigue[c]	28	1.1
Edema[d]	13	0
Immune system disorders		
Cytokine release syndrome	49	1.1
Infections and infestations[e]		
Bacterial infectious disorders	12	6
Infections with pathogen unspecified	12	6
Sepsis[f]	10	7
Metabolism and nutrition disorders		
Decreased appetite	15	0

Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[g]	36	3.4
Nervous system disorders		
Headache[h]	34	6
Dizziness[i]	20	1.1
Motor dysfunction[j]	12	3.4
Tremor[k]	11	1.1
Psychiatric disorders		
Insomnia[l]	15	0
Respiratory, thoracic and mediastinal disorders		
Cough[m]	11	0
Skin and subcutaneous tissue disorders		
Rash[n]	12	1.1
Vascular disorders		
Hypotension[o]	15	2.2
Hemorrhage[p]	12	0

[a] Tachycardia includes atrial flutter, sinus tachycardia, supraventricular tachycardia, tachycardia.

[b] Abdominal pain includes abdominal pain, abdominal pain lower, abdominal tenderness.

[c] Fatigue includes asthenia, fatigue, malaise.

[d] Edema includes edema peripheral, localized edema, edema peripheral, pleural effusion swelling.

[e] Infections and infestations are grouped per high-level grouped term.

[f] Sepsis includes bacteremia, bacterial sepsis, enterococcal bacteremia, Escherichia bacteremia, Klebsiella bacteremia, Klebsiella sepsis, sepsis, septic shock, staphylococcal bacteremia.

[g] Musculoskeletal pain includes arthralgia, back pain, bone pain, flank pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, osteoarthritis, pain in extremity.

[h] Headache includes headache, migraine, migraine with aura.

[i] Dizziness includes dizziness, dizziness postural, syncope, vertigo.

[j] Motor dysfunction includes fine motor skill dysfunction, muscle spasms, muscular weakness.

[k] Tremor includes resting tremor, tremor, essential tremor.

[l] Insomnia includes insomnia, sleep disorder.

[m] Cough includes cough, productive cough.

[n] Rash includes catheter site rash, dermatitis acneiform, dermatitis exfoliative generalized, erythema multiforme, rash, rash maculo-papular, rash pruritic.

[o] Hypotension includes hypotension, orthostatic hypotension.

[p] Hemorrhage includes conjunctival hemorrhage, cystitis hemorrhagic, epistaxis, gastrointestinal hemorrhage, hematoma, hematuria, retinal hemorrhage, vaginal hemorrhage.

Other clinically important adverse reactions in < 10% of patients treated with BREYANZI included the following:

- *Immune system disorders:* Hemophagocytic lymphohistiocytosis (1.1%)
- *Infections and infestations:* Viral infection (9%), fungal infection (4.5%), pneumonia (2.2%)
- *Nervous system disorders:* Encephalopathy (8%), aphasia (4.5%), peripheral neuropathy (4.5%), ataxia (3.4%), paresis (1.1%)
- *Psychiatric disorders:* Delirium (2.2%)
- *Renal and urinary disorders:* Renal failure (3.4%)
- *Respiratory, thoracic, and mediastinal disorders:* Dyspnea (8%)
- *Vascular disorders:* Thrombosis (8%), hypertension (7%)

Table 5: Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients Treated with BREYANZI in the TRANSFORM Study

Laboratory Abnormality[a]	**Grade 3 or 4 (%)[b]**
Lymphocyte count decreased	98
Neutrophil count decreased	89
Platelet count decreased	48
Hemoglobin decreased	32

[a] Baseline lab values were assessed prior to lymphodepleting chemotherapy.
[b] Based on 88 evaluable patients, defined as those with both a baseline grade and at least one post-baseline grade for the particular lab.

Grade 4 laboratory abnormalities in ≥ 10% of patients were lymphocyte decrease (64%), neutrophil decrease (66%), and platelet decrease (34%).

PILOT

The safety of BREYANZI was evaluated in the PILOT study, a single-arm open-label study in transplant-ineligible patients with R/R LBCL after one line of chemoimmunotherapy *[see Clinical Studies (14.1)]*. The study enrolled patients who were ineligible for high-dose therapy and autologous HSCT due to organ function or age, but who had adequate organ function for CAR-T cell therapy. Patients with a history of relevant CNS disorders (such as seizures or cerebrovascular ischemia), ECOG performance status > 2, or uncontrolled infection were ineligible. The trial required left ventricular ejection fraction ≥ 40%, adequate oxygen saturation on room air with ≤ Grade 1 dyspnea, AST and ALT ≤ 5 x ULN, total bilirubin < 2.0 mg/dL, creatinine clearance > 30 mL/min, and adequate bone marrow function to receive lymphodepleting chemotherapy. The planned dose of BREYANZI was 100×10^6 CAR-positive viable T cells.

The median age was 74 years (range: 53 to 84 years), 90% were age ≥ 65 years, 61% were male. The ECOG performance status was 0 or 1 in 74% of patients and 2 in 26% of patients; 25% had CrCl < 60 ml/min; 20% had a baseline ANC < 1000/µL.

Serious adverse reactions occurred in 33% of patients. The most common nonlaboratory, serious adverse reactions (> 2%) were CRS, confusional state, gastrointestinal hemorrhage, muscular weakness, musculoskeletal pain, pulmonary embolism, and sepsis.

Table 6 presents selected nonlaboratory adverse reactions, and Table 7 describes selected new or worsening Grade 3 or 4 laboratory abnormalities.

The most common nonlaboratory adverse reactions (≥ 20%) were fatigue, CRS, fever,

nausea, encephalopathy, hypotension, musculoskeletal pain, and edema.

Table 6: Adverse Reactions in ≥ 10% of Patients Treated with BREYANZI in the PILOT Study (N=61)

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
Cardiac disorders		
Tachycardia[a]	10	0
Gastrointestinal disorders		
Nausea	25	1.6
Diarrhea	15	0
Constipation	11	0
General disorders and administration site conditions		
Fatigue[b]	44	1.6
Fever	38	1.6
Edema[c]	20	0
Immune system disorders		
Cytokine release syndrome	39	1.6
Infections and infestations		
Infections with pathogen unspecified[d]	13	4.9
Upper respiratory tract infection[e]	13	0
Bacterial infectious disorders	10	3.3
Metabolism and nutrition disorders		
Decreased appetite	13	1.6
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[f]	23	4.9
Nervous system disorders		
Encephalopathy[g]	23	4.9
Dizziness[h]	16	1.6
Tremor[i]	16	0
Headache	11	1.6
Psychiatric disorders		
Insomnia	11	0
Respiratory, thoracic and mediastinal disorders		
Cough[j]	18	0
Dyspnea[k]	16	4.9
Vascular disorders		
Hypotension[l]	23	1.6
Hypertension	10	4.9

[a] Tachycardia includes atrial fibrillation, sinus tachycardia, tachycardia.

[b] Fatigue includes asthenia, fatigue, malaise.

[c] Edema includes edema peripheral, pleural effusion, swelling.

[d] Grouped per high-level grouped term.

[e] Upper respiratory tract infection includes nasal congestion, paranasal sinus

hypersecretion, rhinitis, rhinorrhea, upper respiratory tract infection.
[f] Musculoskeletal pain includes arthralgia, back pain, bone pain, flank pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, osteoarthritis, pain in extremity, spinal pain.
[g] Encephalopathy includes amnesia, apraxia, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, dyscalculia, encephalopathy, lethargy, memory impairment, mental status changes, somnolence.
[h] Dizziness includes dizziness, dizziness postural, syncope, vertigo.
[i] Tremor includes resting tremor, tremor.
[j] Cough includes cough, productive cough.
[k] Dyspnea includes acute respiratory distress syndrome, dyspnea, tachypnea, wheezing.
[l] Hypotension includes hypotension, orthostatic hypotension.

Other clinically important adverse reactions in < 10% of patients included the following:

- *Blood and lymphatic system disorders:* Febrile neutropenia (1.6%)
- *Eye disorders:* Vision blurred (3.3%)
- *Gastrointestinal disorders:* Vomiting (8%), abdominal pain (7%), gastrointestinal hemorrhage (4.9%)
- *Infections and infestations:* Fungal infection (4.9%), sepsis (3.3%), viral infection (3.3%)
- *Nervous system disorders:* Motor dysfunction (7%), aphasia (4.9%), ataxia (4.9%), peripheral neuropathy (4.9%)
- *Psychiatric disorders:* Delirium (3.3%)
- *Renal and urinary disorders:* Renal failure (7%)
- *Respiratory, thoracic, and mediastinal disorders:* Hypoxia (4.9%)
- *Skin and subcutaneous tissue disorders:* Rash (7%)
- *Vascular disorders:* Thrombosis (7%)

Table 7: Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients Treated with BREYANZI in the PILOT Study (N=61)

Laboratory Abnormality[a]	**Grade 3 or 4 (%)**
Lymphocyte count decreased	97
Neutrophil count decreased	80
Hemoglobin decreased	30
Platelet count decreased	26

[a] Baseline lab values were assessed prior to lymphodepleting chemotherapy.

Grade 4 laboratory abnormalities in ≥ 10% of patients were lymphocyte decrease (95%), neutrophil decrease (57%), and platelet decrease (20%).

Relapsed or Refractory LBCL After Two or More Lines of Therapy

TRANSCEND

The safety of BREYANZI was evaluated in the TRANSCEND study, in which 268 adult patients with R/R LBCL after 2 or more prior lines of therapy received a single dose of

CAR-positive viable T cells *[see Clinical Studies (14.1)]*. Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia) or autoimmune disease requiring systemic immunosuppression were ineligible. The median age of the study population was 63 years (range: 18 to 86 years); 65% were male. The Eastern Cooperative Oncology Group (ECOG) performance status at screening was 0 in 41% of patients, 1 in 58% of patients, and 2 in 1.5% of patients.

Serious adverse reactions occurred in 46% of patients. The most common nonlaboratory, serious adverse reactions (> 2%) were CRS, encephalopathy, sepsis, febrile neutropenia, aphasia, pneumonia, fever, hypotension, dizziness, and delirium. Fatal adverse reactions occurred in 4% of patients.

Table 8 presents selected nonlaboratory adverse reactions reported in patients treated with BREYANZI, and Table 9 describes selected new or worsening Grade 3 or 4 laboratory abnormalities.

The most common nonlaboratory adverse reactions (≥ 20%) were fatigue, CRS, musculoskeletal pain, nausea, headache, encephalopathy, infections (pathogen unspecified), decreased appetite, diarrhea, hypotension, tachycardia, dizziness, cough, constipation, abdominal pain, vomiting, and edema.

Table 8: Adverse Reactions in ≥ 10% of Patients Treated with BREYANZI in the TRANSCEND Study (N=268)

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
Cardiac disorders		
Tachycardia[a]	25	0
Gastrointestinal disorders		
Nausea	33	1.5
Diarrhea	26	0.4
Constipation	23	0
Abdominal pain[b]	21	3.0
Vomiting	21	0.4
General disorders and administration site conditions		
Fatigue[c]	48	3.4
Edema[d]	21	1.1
Fever	16	0
Chills	12	0
Immune system disorders		
Cytokine release syndrome	46	4.1
Infections and infestations[e]		
Infection with pathogen unspecified[f]	29	16
Bacterial infection[g]	13	5
Upper respiratory tract infection[h]	13	0.7
Viral infection	10	1.5
Metabolism and nutrition disorders		
Decreased appetite	28	2.6

Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[i]	37	2.2
Nervous system disorders		
Headache[j]	30	1.1
Encephalopathy[k]	29	9
Dizziness[l]	24	2.6
Tremor[m]	16	0
Peripheral neuropathy[n]	11	0
Aphasia[o]	10	2.2
Motor dysfunction[p]	10	1.1
Psychiatric disorders		
Insomnia[q]	14	0.4
Anxiety[r]	10	0
Delirium[s]	10	2.2
Renal and urinary disorders		
Renal failure[t]	11	3.0
Respiratory, thoracic, and mediastinal disorders		
Cough[u]	23	0
Dyspnea[v]	16	2.6
Skin and subcutaneous tissue disorders		
Rash[w]	13	0.4
Vascular disorders		
Hypotension[x]	26	3.4
Hypertension	14	4.5
Hemorrhage[y]	10	1.5

a Tachycardia includes heart rate increased, sinus tachycardia, tachycardia.

b Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness.

c Fatigue includes asthenia, fatigue, malaise.

d Edema includes edema, edema peripheral, fluid overload, fluid retention, generalized edema, hypervolemia, peripheral swelling, pulmonary congestion, pulmonary edema, swelling.

e Infections and infestations are grouped by pathogen type and selected clinical syndromes.

f Infections with pathogen unspecified contains febrile neutropenia (9%).

g Bacterial infection includes infections by pathogen type plus appendicitis, diverticulitis, peritonitis, skin infection, tooth infection.

h Upper respiratory tract infections include nasopharyngitis, pharyngitis, rhinitis, rhinovirus infection, sinusitis, upper respiratory tract congestion, upper respiratory tract infection.

i Musculoskeletal pain includes arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, pain in extremity, spinal pain.

j Headache includes headache, head discomfort, migraine, sinus headache.

k Encephalopathy includes amnesia, bradyphrenia, cognitive disorder, confusional state, depersonalization/derealization disorder, depressed level of consciousness, disturbance

in attention, encephalopathy, flat affect, hypersomnia, incoherent, lethargy, leukoencephalopathy, loss of consciousness, memory impairment, mental impairment, mental status changes, somnolence.

l Dizziness includes dizziness, presyncope, syncope, vertigo.

m Tremor includes essential tremor, resting tremor, tremor.

n Peripheral neuropathy includes hyperesthesia, hypoesthesia, meralgia paresthetica, neuralgia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, sciatica, sensory loss.

o Aphasia includes aphasia, disorganized speech, dysarthria, dysphemia, dysphonia, slow speech, speech disorder.

p Motor dysfunction includes eyelid ptosis, motor dysfunction, muscle rigidity, muscle spasms, muscle spasticity, muscle tightness, muscle twitching, muscular weakness, myoclonus, myopathy.

q Insomnia includes insomnia, somnambulism.

r Anxiety includes anxiety, panic attack.

s Delirium includes agitation, delirium, delusion, disorientation, hallucination, 'hallucination, visual', irritability, restlessness.

t Renal failure includes acute kidney injury, blood creatinine increased, chronic kidney disease, renal failure, renal injury.

u Cough includes cough, productive cough, upper-airway cough syndrome.

v Dyspnea includes acute respiratory failure, dyspnea, dyspnea exertional, respiratory failure.

w Rash includes erythema, dermatitis acneiform, perineal rash, rash, rash erythematous, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic, rash pustular.

x Hypotension includes hypotension, orthostatic hypotension.

y Hemorrhage includes catheter site hemorrhage, conjunctival hemorrhage, epistaxis, hematoma, hematuria, hemorrhage, hemorrhage intracranial, pulmonary hemorrhage, retinal hemorrhage, vaginal hemorrhage.

Other clinically important adverse reactions in < 10% of patients included the following:

- *Cardiac disorders:* Arrhythmia (6%), cardiomyopathy (1.5%)
- *Gastrointestinal disorders:* Gastrointestinal hemorrhage (4.1%)
- *Infections and infestations:* Pneumonia (8%), fungal infection (8%), sepsis (4.5%), urinary tract infection (4.1%)
- *Metabolism and nutrition disorders:* Tumor lysis syndrome (0.7%)
- *Nervous system disorders:* Ataxia or gait disturbance (7%), visual disturbance (5%), paresis (2.6%), cerebrovascular events (1.9%), seizure (1.1%), brain edema (0.4%)
- *Procedural complications:* Infusion-related reaction (1.9%)
- *Respiratory, thoracic, and mediastinal disorders:* Pleural effusion (7%), hypoxia (6%)
- *Vascular disorder:* Thrombosis (7%)

Table 9: Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients Treated with BREYANZI in the TRANSCEND Study

Laboratory Abnormality[a]	**Grade 3 or 4 (%)[b]**
Lymphocyte count decreased	95

Neutrophil count decreased	88
Platelet count decreased	41
Hemoglobin decreased	32
Phosphate decreased	16
Fibrinogen decreased	14

a Baseline lab values were assessed prior to lymphodepleting chemotherapy.
b The denominator varied from 239 to 268, based on the number of patients with a baseline value and at least one post-treatment value for the particular lab.

Relapsed or Refractory CLL/SLL

TRANSCEND-CLL

The safety of BREYANZI was evaluated in the TRANSCEND-CLL study, which included 89 adult patients with R/R CLL/SLL who had received at least 2 prior lines of therapy including a BTK inhibitor and a BCL-2 inhibitor before receiving a single dose of CAR-positive viable T cells *[see Clinical Studies (14.2)]*. Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia) or autoimmune disease requiring systemic immunosuppression, Richter's transformation, ECOG performance status >1 were ineligible. The trial required left ventricular ejection fraction ≥ 40%, adequate oxygen saturation on room air with ≤ Grade 1 dyspnea, ALT ≤ 5 x ULN, total bilirubin < 2.0 mg/dL, creatinine clearance > 30 mL/min, and adequate bone marrow function to receive lymphodepleting chemotherapy.

The median age of the study population was 66 years (range: 49 to 82 years); 69% were male, 84% were white, 3% were black, 1% were Asian. Two percent were Hispanic, and 89% were non-Hispanic. The Eastern Cooperative Oncology Group (ECOG) performance status at screening was 0 in 40% of patients, and 1 in 60% of patients.

Serious adverse reactions occurred in 60% of patients. The most common nonlaboratory serious adverse reactions (> 2%) were CRS, encephalopathy, febrile neutropenia, pneumonia, hemorrhage, fever, renal failure, aphasia, abdominal pain, delirium, tumor lysis syndrome, upper respiratory tract infection, and hemophagocytic lymphohistiocytosis [IEC-HS]. Fatal adverse reactions occurred in 1.1 % of patients.

Table 10 presents selected nonlaboratory adverse reactions reported in patients treated with BREYANZI, and Table 11 describes selected new or worsening Grade 3 or 4 laboratory abnormalities.

The most common nonlaboratory adverse reactions (≥ 20%) were CRS, encephalopathy, fatigue, musculoskeletal pain, nausea, edema, diarrhea, dyspnea, headache, fever, decreased appetite, constipation, tremor, dizziness, Infection with pathogen unspecified, rash, tachycardia, cough, and delirium.

Table 10: Adverse Reactions in ≥ 10% of Patients Treated with BREYANZI in the TRANSCEND-CLL Study (N=89)

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
Blood and lymphatic system disorders		
Febrile neutropenia	12	12
Cardiac disorders		

Tachycardia[a]	21	0
Gastrointestinal disorders		
Nausea	35	0
Diarrhea[b]	30	1.1
Constipation	24	0
Abdominal pain[c]	18	0
Vomiting	15	0
General disorders and administration site conditions		
Fatigue[d]	40	4.5
Edema[e]	30	4.5
Fever[f]	27	1.1
Chills	17	1.1
Immune system disorders		
Cytokine release syndrome	83	9
Infections and infestations		
Infection with pathogen unspecified[g]	23	10
Upper respiratory tract infection[h]	19	1.1
Viral infection[g]	10	1.1
Metabolism and nutrition disorders		
Decreased appetite	27	4.5
Tumor lysis syndrome	11	11
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[i]	42	1.1
Nervous system disorders		
Encephalopathy[j]	44	18
Headache[k]	28	1.1
Tremor	24	2.2
Dizziness[l]	21	1.1
Motor dysfunction[m]	14	2.2
Peripheral neuropathy[n]	12	0
Taste disorder[o]	10	0
Psychiatric disorders		
Delirium[p]	20	3.4
Insomnia	16	1.1
Anxiety	12	1.1
Renal and urinary disorders		
Renal failure[q]	15	3.4
Respiratory, thoracic, and mediastinal disorders		
Dyspnea[r]	27	8
Cough[s]	20	0
Skin and subcutaneous tissue disorders		
Rash[t]	23	2.2
Vascular disorders		

Hypotension[u]	17	0
Hemorrhage[v]	16	1.1
Hypertension	10	4.5

[a] Tachycardia includes atrial fibrillation, atrial flutter, sinus tachycardia, tachycardia, ventricular tachycardia.
[b] Diarrhea includes diarrhea
[c] Abdominal pain includes abdominal pain, abdominal tenderness.
[d] Fatigue includes asthenia, fatigue, malaise.
[e] Edema includes ascites, face edema, hypervolemia, edema peripheral, pleural effusion, pulmonary edema, scrotal edema.
[f] Fever includes pyrexia.
[g] Grouped per high-level grouped term.
[h] Upper respiratory tract infection includes acute sinusitis, nasal congestion, nasopharyngitis, rhinitis, rhinovirus infection, sinusitis, upper respiratory tract infection.
[i] Musculoskeletal pain includes arthralgia, arthritis, back pain, bone pain, flank pain, musculoskeletal chest pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity.
[j] Encephalopathy includes cognitive disorder, confusional state, disturbance in attention, encephalopathy, lethargy, memory impairment, mental status changes, somnolence.
[k] Headache includes headache, sinus headache.
[l] Dizziness includes dizziness, presyncope, syncope, vertigo.
[m] Motor dysfunction includes asterixis, muscle spasms, muscular weakness, myoclonus.
[n] Peripheral neuropathy includes hyperaesthesia, hypoaesthesia, neuralgia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy.
[o] Taste disorder includes dysgeusia, taste disorder.
[p] Delirium includes agitation, delirium, hallucination, hallucination visual, intensive care unit delirium, irritability, restlessness.
[q] Renal failure includes acute kidney injury, chronic kidney disease, renal failure.
[r] Dyspnea includes dysponea, respiratory failure, tachypnoea, wheezing.
[s] Cough includes cough, productive cough, upper-airway cough syndrome.
[t] Rash includes dermatitis contact, erythema, petechiae, rash, rash macular, rash maculo-papular, scrotal erythema, seborrhoeic keratosis, urticaria.
[u] Hypotension includes hypotension, orthostatic hypotension.
[v] Hemorrhage includes epistaxis, haemorrhage intracranial, haematoma, haematuria, haemorrhoidal haemorrhage, intraventricular haemorrhage, lower gastrointestinal haemorrhage, traumatic haemothorax.

Other clinically important adverse reactions in < 10% of patients included the following:

- *Cardiac disorders:* Chest discomfort (4.5%), Arrhythmia (2.2%).
- *Eye disorders:* Vision blurred (4.5%).
- *Gastrointestinal disorders:* Dyspepsia (9%), abdominal distension (7%).
- *Immune system disorders:* Hemophagocytic lymphohistiocytosis [IEC-HS] (3.4%).
- *Infections and infestations*: Fungal infection (9%), pneumonia (7%), urinary tract infection (7%), bacterial infectious disorders (4.5%), sepsis (2.2%).
- *Injury, poisoning and procedural complications:* Infusion related reaction (1.1%).

- *Nervous system disorders*: Aphasia (8%), Ataxia (3.4%), Paresis (3.4%), Seizure (1.1%).
- *Psychiatric disorders:* Affective disorder (7%).
- *Respiratory, thoracic and mediastinal disorders*: Oral pain (8%), hypoxia (8%).
- *Skin and subcutaneous tissue disorders:* Ecchymosis (8%), xerosis (7%), pruritus (6%).
- *Vascular disorder:* Thrombosis (6%).

Table 11: Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients Treated with BREYANZI in the TRANSCEND-CLL Study

Laboratory Abnormality[a]	**Grade 3 or 4 (%)**[b]
Neutrophil count decreased	**94**
Lymphocyte count decreased	87
White blood cell decreased	85
Platelet count decreased	53
Hemoglobin decreased	49
Hypophosphatemia	24
Hyponatremia	18
Hypocalcemia	11

[a] Baseline lab values were assessed prior to lymphodepleting chemotherapy.

[b] The denominator ranged from 85 to 89 for other measurements, based on the number of patients with a baseline value and at least one post-treatment value for the particular lab.

Grade 4 laboratory abnormalities in ≥ 10% of patients were neutrophil count decreased (81%), lymphocyte count decreased (73%), white blood cell decreased (72%), and platelet count decrease (30%).

6.2 Immunogenicity

BREYANZI has the potential to induce anti-product antibodies. The immunogenicity of BREYANZI has been evaluated using an electrochemiluminescence (ECL) immunoassay for the detection of binding antibodies against the extracellular CD19-binding domain of BREYANZI. Pre-existing anti-product antibodies were detected in 11% (28/261) in TRANSCEND, 1% (1/89) in TRANSFORM, 0% (0/51) in PILOT, and 2% (2/86) in TRANSCEND-CLL, of patients. Treatment-induced or treatment-boosted anti-product antibodies were detected in 11% (27/257) in TRANSCEND, 1% (1/89) in TRANSFORM, 2% (1/49) in PILOT, and 7% (6/84) in TRANSCEND-CLL, of patients. Due to the small number of patients who had anti-product antibodies, the relationship between anti-product antibody status and efficacy, safety, or pharmacokinetics was not conclusive.

6.3 Postmarketing Experience

Because adverse events to marketed products are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure.

The following adverse events have been identified during postmarketing use of BREYANZI.

Nervous System Disorder: Immune effector cell-associated neurotoxicity syndrome (ICANS).

Neoplasms: T cell malignancies

7 DRUG INTERACTIONS

7.1 Drug-Laboratory Test Interactions

HIV and the lentivirus used to make BREYANZI have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests may yield false-positive results in patients who have received BREYANZI.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with BREYANZI use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with BREYANZI to assess whether it can cause fetal harm when administered to a pregnant woman.

It is not known if BREYANZI has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia and hypogammaglobulinemia. Therefore, BREYANZI is not recommended for women who are pregnant, and pregnancy after BREYANZI infusion should be discussed with the treating physician.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of BREYANZI in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for BREYANZI and any potential adverse effects on the breastfed infant from BREYANZI or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy status of females with reproductive potential should be verified. Sexually active females of reproductive potential should have a pregnancy test prior to starting treatment with BREYANZI.

Contraception

See the prescribing information for fludarabine and cyclophosphamide for information

on the need for effective contraception in patients who receive lymphodepleting chemotherapy.

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

Infertility

There are no data on the effects of BREYANZI on fertility.

8.4 Pediatric Use

The safety and efficacy of BREYANZI have not been established in pediatric patients.

8.5 Geriatric Use

In clinical trials of BREYANZI, 111 (41%) of 268 patients with two or more prior lines of therapy for LBCL, and 89 (59%) of 150 patients with one prior line of therapy for LBCL, were 65 years of age or older; 27 (10%) and 28 (19%) were 75 years of age or older, respectively. In patients with CLL/SLL, 51 (57%) of 89 were 65 years of age or older, and 9 (10%) were 75 years of age or older. No clinically important differences in safety or effectiveness of BREYANZI were observed between patients aged ≥ 65 and younger patients.

11 DESCRIPTION

BREYANZI (lisocabtagene maraleucel) is a CD19-directed genetically modified autologous T cell immunotherapy administered as a defined composition of CAR-positive viable T cells (consisting of CD8 and CD4 components). The CAR is comprised of the 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. In addition, BREYANZI includes a nonfunctional truncated epidermal growth factor receptor (EGFRt) that is co-expressed on the cell surface with the CD19-specific CAR.

BREYANZI is a T cell product. BREYANZI is prepared from the patient's T cells, which are obtained via a standard leukapheresis procedure. The purified CD8-positive and CD4-positive T cells are separately activated and transduced with the replication-incompetent lentiviral vector containing the anti-CD19 CAR transgene. The transduced T cells are expanded in cell culture, washed, formulated into a suspension, and cryopreserved as separate CD8 and CD4 component vials that together constitute a single dose of BREYANZI. The product must pass a sterility test before release for shipping as a frozen suspension in patient-specific vials. The product is thawed prior to administration *[see Dosage and Administration (2.2) and How Supplied/Storage and Handling (16)]*.

The BREYANZI formulation contains 75% (v/v) Cryostor® CS10 [containing 7.5% dimethylsulfoxide (v/v)], 24% (v/v) Multiple Electrolytes for Injection, Type 1, 1% (v/v) of 25% albumin (human).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BREYANZI is a CD19-directed genetically modified autologous cell immunotherapy administered as a defined composition to reduce variability in CD8-positive and CD4-positive T cell dose. The CAR is comprised of an 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 signaling is critical for initiating activation and antitumor activity, while 4-1BB (CD137) signaling enhances the expansion and persistence of BREYANZI.

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

12.2 Pharmacodynamics

Following BREYANZI infusion, pharmacodynamic responses were evaluated over a 4-week period by measuring transient elevation of soluble biomarkers such as cytokines, chemokines, and other molecules. Peak elevation of soluble biomarkers was observed within the first 14 days after BREYANZI infusion and returned to baseline levels within 28 days.

B-cell aplasia, defined as CD19+ B cells comprising less than 3% of peripheral blood lymphocytes, is an on-target effect of BREYANZI. B-cell aplasia was observed in the majority of patients for up to 1 year following BREYANZI infusion.

12.3 Pharmacokinetics

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

Relapsed or Refractory LBCL

The median time of maximal expansion in peripheral blood occurred 10-12 days after infusion. BREYANZI was present in peripheral blood for an estimated median of 12.1 months (range: 0.1+ to 24.2+ months).

Among patients who received two or more prior lines of therapy for LBCL (TRANSCEND), responders (N=135) had a 2.3-fold higher median C_{max} than nonresponders (N=37) (35,335 vs. 15,527 copies/µg). Responders had a 1.8-fold higher median $AUC_{0\text{-}28d}$ than nonresponders (273,552 vs. 155,240 day*copies/µg).

In TRANSCEND, patients with higher CAR-T cell expansion tended to have higher rates of CRS and neurologic toxicities. Patients treated with tocilizumab (N=49) had a 3.6-fold and 3.7-fold higher median C_{max} and $AUC_{0\text{-}28d}$, respectively, compared to patients who did not receive tocilizumab (N=189). Similarly, patients who received corticosteroids (N=50) had a 3.8-fold and 3.7-fold higher median C_{max} and $AUC_{0\text{-}28d}$, respectively, compared to patients who did not receive corticosteroids (N=188).

Patients < 65 years old (N=142) had a 3.1-fold and 2.3-fold higher median C_{max} and $AUC_{0\text{-}28d}$, respectively, compared to patients ≥ 65 years old (N=96). Sex, race, ethnicity, and body weight did not show clear relationships to C_{max} and $AUC_{0\text{-}28d}$.

Relapsed or Refractory CLL/SLL

The median time of maximal expansion in peripheral blood occurred 14 days after infusion. BREYANZI was present in peripheral blood for an estimated median of 12.0

months (range: 0.1+ to 30.1+ months).

Among patients who received prior therapy for CLL/SLL (TRANSCEND-CLL), responders (N=27) had a 2.0-fold higher median C_{max} than nonresponders (N=25) (99,559 vs. 48,948 copies/µg). Responders had a 1.9-fold higher median $AUC_{0\text{-}28d}$ than nonresponders (793,893 vs. 408,307 day*copies/µg).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with BREYANZI. No studies have been conducted to evaluate the effects of BREYANZI on fertility. *In vitro* studies with BREYANZI manufactured from healthy donors and patients showed no evidence for transformation and/or immortalization and no preferential integration near genes associated with oncogenic transformation.

14 CLINICAL STUDIES

14.1 Relapsed or Refractory Large B-Cell Lymphoma

Relapsed or Refractory LBCL After One Line of Therapy

TRANSFORM

A randomized, open-label, multicenter trial evaluated the efficacy of BREYANZI in adult patients with relapsed or refractory LBCL after first-line chemoimmunotherapy (TRANSFORM; NCT03575351). Patients had not yet received treatment for relapsed or refractory lymphoma, were potential candidates for autologous HSCT, and were required to have primary refractory disease or relapse within 12 months from complete response (CR) to initial chemoimmunotherapy. Eligibility criteria required adequate organ function and blood counts for HSCT.

In total, 184 patients were randomized in a 1:1 ratio to receive a single infusion of BREYANZI (planned dose, 100×10^6 CAR-positive viable T cells) or to receive standard therapy consisting of 3 cycles of chemoimmunotherapy followed by high-dose therapy and autologous HSCT in patients who attained CR or PR. All patients underwent leukapheresis prior to randomization.

Patients randomized 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. Bridging chemotherapy was permitted between leukapheresis and the start of lymphodepleting chemotherapy. BREYANZI was administered in the inpatient (79%) and outpatient (21%) setting.

In the overall study population, the median age was 59 years (range: 20 to 75 years), 57% were male, 59% were white, 10% were Asian, and 4% were black. Diagnoses included de novo DLBCL NOS (55%), high-grade B-cell lymphoma (23%), primary mediastinal large B-cell lymphoma (10%), and DLBCL arising from indolent lymphoma (8%). Of these patients, 73% had primary refractory disease to last therapy and 27% had relapsed disease within 12 months of achieving CR to first-line therapy.

Of 92 patients randomized to receive BREYANZI, 89 (97%) received BREYANZI. The median time from leukapheresis to product availability was 26 days (range: 19 to 84 days), and the median time from leukapheresis to product infusion was 36 days (range: 25 to 91 days). Fifty-eight (63%) patients received bridging therapy. One patient received a nonconforming product (manufacturing failure; 1.1%).

Of the 92 patients randomized to receive standard therapy, 91 started treatment and 43 (47%) received high-dose therapy and HSCT. The most common reason for not receiving HSCT was lack of efficacy of the salvage chemotherapy.

The primary efficacy measure was event-free survival (EFS) as determined by an independent review committee (IRC). Other efficacy measures included progression-free survival. Efficacy is summarized in Table 12 and Figure 1. The estimated 1-year EFS was 45% [95% CI: 29, 59] in the BREYANZI arm and 24% [95% CI: 14, 35] in the standard therapy arm.

Of the 92 patients in the BREYANZI arm, the estimated median DOR was not reached (95% CI: 7.9 months, NR) in patients who achieved CR (N=61) and 2.3 months (95% CI: 2.1, NR) in patients who achieved a best response of PR (N=18).

An interim analysis of overall survival was conducted at the time of the primary EFS analysis. The interim analysis of overall survival did not meet the criteria for statistical significance. Forty-six patients randomized to the standard therapy arm (50%) subsequently received BREYANZI on protocol.

Table 12: Efficacy Results in Patients with Relapsed or Refractory LBCL (TRANSFORM Study)

Outcome[a]	**BREYANZI Arm (N=92)**	**Standard Therapy Arm (N=92)**
Event-Free Survival[b]		
Number of events, n (%)	35 (38)	63 (69)
Median, months [95% CI][c]	10.1 [6.1, NR]	2.3 [2.2, 4.3]
Hazard ratio [95% CI][d]	0.34 [0.22, 0.52]	
One-sided p-value	<0.0001[f]	
Complete Response Rate, % [95% CI]	66 [56, 76]	39 [29, 50]
Difference in CR rate, % [95% CI]	27 [12, 41]	
One-sided p-value[e]	<0.0001[f]	
Progression-Free Survival		
Number of events, n (%)	28 (30)	43 (47)
Median, months [95% CI][c]	14.8 [6.6, NR]	5.7 [3.9, 9.4]
Hazard ratio [95% CI][d]	0.41 [0.25, 0.66]	
One-sided p-value	0.0001[f]	

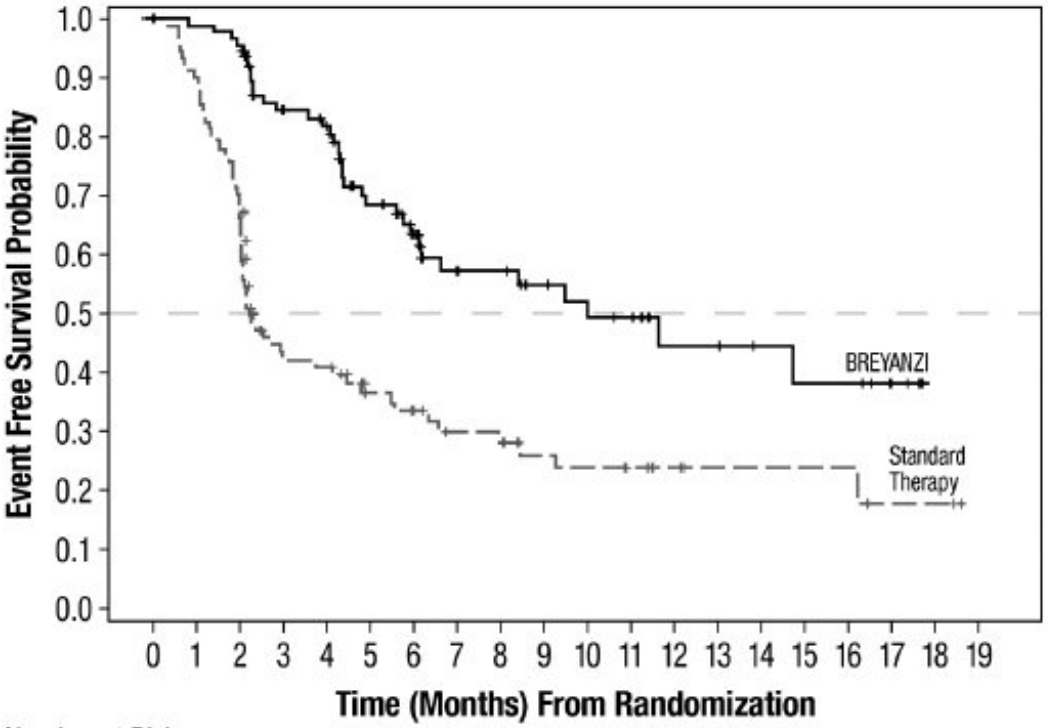
NR=not reached; CI=confidence interval.

a Per the Lugano criteria, as assessed by an IRC.

b EFS is defined as time from randomization to the earliest date of disease progression or relapse, death from any cause, failure to achieve CR or PR by 9 weeks post-randomization, or start of new lymphoma therapy due to efficacy concerns.

c Kaplan-Meier estimate.
d Based on a stratified Cox proportional hazards model. For all stratified analyses, stratification was based on response to first-line therapy (primary refractory vs relapsed) and second-line age-adjusted International Prognostic Index.
e Cochran-Mantel-Haenszel test.
f p-value is compared with 0.012 of the allocated alpha for this pre-specified interim analysis.

Figure 1: Kaplan-Meier Plot of IRC-Assessed Event-Free Survival (Intention-to- Treat Analysis)



Number at Risk

Standard Therapy	92	83	66	35	32	23	21	16	16	12	11	10	6	4	4	4	4	2	2	0
BREYANZI	92	89	86	66	62	43	36	27	26	21	19	17	9	9	7	6	6	4	0	

PILOT

The efficacy of BREYANZI was evaluated in a single-arm, open-label, multicenter trial (PILOT; NCT03483103) in transplant-ineligible patients with relapsed or refractory LBCL after one line of chemoimmunotherapy. The study enrolled patients who were not eligible for high-dose therapy and autologous HSCT due to organ function or age, while also having adequate organ function for CAR-T cell therapy. The study required at least one of the following criteria: age ≥ 70 years, adjusted diffusing capacity of the lung for carbon monoxide (DLCO) ≤ 60%; LVEF < 50%; creatinine clearance < 60mL/min; AST or ALT greater than 2 × ULN, or ECOG performance status of 2. The planned dose of BREYANZI was 100×10^6 CAR-positive viable T cells. Bridging therapy for disease control was permitted between leukapheresis and the start of lymphodepleting

chemotherapy. Of the 61 patients treated with BREYANZI, 32 (53%) received bridging therapy.

BREYANZI was administered 2 to 7 days following completion of lymphodepleting chemotherapy. The lymphodepleting chemotherapy regimen consisted of fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day concurrently for 3 days. BREYANZI was administered in the inpatient (67%) and outpatient (33%) setting.

Of 74 patients who underwent leukapheresis, 61 (82%) received BREYANZI and comprise the main efficacy population; 1 (1.4%) received CAR-positive T cells that did not meet the product specifications for BREYANZI (manufacturing failure); and 12 (16%) did not receive CAR-positive T cells for other reasons.

Of the 61 patients who received BREYANZI, the median age was 74 years (range: 53 to 84 years), 61% were male, 89% were white, 3% were Asian, and 2% were black. Diagnoses included de novo DLBCL NOS (51%), high-grade B-cell lymphoma (33%), and DLBCL arising from follicular lymphoma (15%). Of these patients, 53% had primary refractory disease, 23% had relapse within 12 months of completing first-line therapy, and 25% had relapse >12 months after first-line therapy.

Efficacy was based on complete response (CR) rate and duration of response (DOR), as determined by an independent review committee (IRC) using 2014 Lugano criteria (Tables 13 and 14). The median time to CR was 1 month (range 0.8 to 6.9 months).

Table 13: Response Rate in Relapsed or Refractory LBCL (PILOT Study)

Outcome[a]	**BREYANZI-Treated (N=61)**	**All Leukapheresed Patients (N=74)**
Overall Response, n (%) [95% CI][b]	49 (80%) [68%, 89%]	50 (68%) [56%, 78%]
Complete Response [95% CI]	33 (54%) [41%, 67%]	34 (46%) [34%, 58%]
Partial Response [95% CI]	16 (26%) [16%, 39%]	16 (22%) [13%, 33%]

CI=confidence interval; NR=Not reached

[a] Per the Lugano criteria, as assessed by an IRC.

[b] 2-sided 95% exact Clopper-Pearson confidence intervals.

Table 14: Duration of Response in the PILOT Study

Outcome[a]	**BREYANZI-Treated (N=61)**
Number of Responders	**49**
DOR	
Median [95% CI], months[b]	11.2 [5.1, NR]
Range, months	0.0+ to 22.8$^+$
DOR if Best Response is CR	
Median [95% CI], months	NR [11.2, NR]
Range, months	2.0+ to 22.8$^+$
Rate at 6 months [95% CI][c]	83% [64, 93]

Rate at 12 months [95% CI][c]	68% [45, 83]
DOR if Best Response is PR	
Median [95% CI], months	2.1 [1.4, 2.3]
Range, months	0.0+ to 7.9
Rate at 6 months [95% CI][c]	8.2% [0.5, 30.5]

DOR=duration of response; CI=confidence interval; CR=complete response; PR=partial response; NR=not reached.

[a] Per the Lugano criteria, as assessed by an IRC.

[b] Kaplan-Meier method is used to obtain 2-sided 95% confidence intervals.

[c] Kaplan-Meier estimate.

+ Indicates a censored value.

Relapsed or Refractory LBCL After Two or More Lines of Therapy

TRANSCEND

The efficacy of BREYANZI was evaluated in an open-label, multicenter, single-arm trial (TRANSCEND; NCT02631044) in adult patients with relapsed or refractory large B-cell non-Hodgkin lymphoma after at least 2 lines of therapy. The study included patients with ECOG performance status ≤ 2, prior autologous and/or allogeneic HSCT, and secondary CNS lymphoma involvement. 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. Bridging therapy for disease control was permitted between apheresis and the start of lymphodepleting chemotherapy, including intrathecal chemotherapy or radiation therapy for treatment of CNS involvement with lymphoma.

BREYANZI was administered 2 to 7 days following completion of lymphodepleting chemotherapy. The lymphodepleting chemotherapy regimen consisted of fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day concurrently for 3 days. BREYANZI was administered in the inpatient and outpatient setting.

Of 299 patients who underwent leukapheresis for whom BREYANZI was manufactured in the dose range of 50 to 110 × 10^6 CAR-positive viable T cells:

- 44 (15%) did not receive CAR-positive T cells either due to manufacturing failures (n=2), death (n=29), disease complications (n=6), or other reasons (n=7).
- 204 (68%) received BREYANZI in the intended dose range, of whom 192 were evaluable for efficacy (main efficacy population); 12 were not evaluable due to absence of PET positive disease at study baseline or after bridging therapy.
- 51 (17%) either received BREYANZI outside of the intended dose range (n=26) or received CAR-positive T cells that did not meet the product specifications for BREYANZI (manufacturing failures; n=25).

Of the 192 patients in the main efficacy population, the median age was 63 years (range: 18 to 86 years), 69% were male, 84% were white, 6% were black, and 4.7% were Asian. The median number of prior therapies was 3 (range: 1 to 8). Diagnoses were de novo DLBCL (53%), DLBCL transformed from indolent lymphoma (25%), high-grade B-cell lymphoma (14%), primary mediastinal large B-cell lymphoma (7%), follicular lymphoma,

grade 3B (1.0%). Of these patients, 64% had disease refractory to last therapy, 53% had primary refractory disease, 37% had prior HSCT and 2.6% had CNS involvement.

Efficacy was based on complete response (CR) rate and duration of response (DOR), as determined by an independent review committee (IRC) using 2014 Lugano criteria (Tables 15 and 16). The median time to first response (CR or partial response [PR]) was 1.0 month (range: 0.7 to 8.9 months). The median time to first CR was 1.0 month (range 0.8 to 12.5 months). Of the 104 patients who achieved CR, 23 initially had stable disease (6 patients) or PR (17 patients), with a median time to improvement of 2.2 months (range: 0.7 to 11.6 months).

Table 15: Response Rate in Main Efficacy Population (TRANSCEND Study)

	BREYANZI-Treated N=192
Overall Response Rate[a], n [95% CI]	141 (73%) [67%, 80%]
Complete Response, n [95% CI]	104 (54%) [47%, 61%]
Partial Response, n [95% CI]	37 (19%) [14%, 26%]

CI=confidence interval.

[a] Per the Lugano criteria, as assessed by an IRC.

Table 16: Duration of Response in the TRANSCEND Study

	BREYANZI-Treated[a] N=192
Number of Responders	**141**
DOR (Months)	
Median [95% CI][b] Range	16.7 [5.3, NR] 0.0^{+} to 23.5^{+}
DOR if Best Response is CR (Months)	
Median [95% CI] Range	NR [16.7, NR] 0.7^{+} to 23.5^{+}
DOR if Best Response is PR (Months)	
Median [95% CI] Range	1.4 [1.1, 2.2] 0.0^{+} to 22.8^{+}

DOR=duration of response; CI=confidence interval; CR=complete response; PR=partial response; NR=not reached.

[a] Evaluable for efficacy.

[b] KM method was used to obtain 2-sided 95% confidence intervals.

$^{+}$ Indicates a censored value.

Response durations were longer in patients who achieved a CR, as compared to patients with a best response of PR (Table 16). Of the 104 patients who achieved CR, 68 (65%) had remission lasting at least 6 months and 64 (62%) had remission lasting at least 9 months.

Of the 287 patients who underwent leukapheresis and had radiographically evaluable disease, 27 additional patients achieved a response, apart from the responses noted in Table 15. The IRC-assessed overall response rate in the leukapheresed population (n=287) was 59% (95% CI: 53, 64), with a CR rate of 43% (95% CI: 37, 49) and PR rate of 15% (95% CI: 11, 20). These efficacy results include responses that may have been contributed solely by bridging therapy, responses after receipt of product outside of the intended dose range, and responses to product that did not meet release specifications.

14.2 Relapsed or Refractory Chronic Lymphocytic Lymphoma or Small Lymphocytic Lymphoma

TRANSCEND-CLL

The efficacy of BREYANZI was evaluated in a phase 1/2, open-label, multicenter, single-arm trial (TRANSCENDCLL; NCT03331198) in adult patients with R/R CLL or SLL who had received at least 2 prior lines of therapy including a BTK inhibitor and a BCL-2 inhibitor. Patients with del(17p), complex karyotype, and unmutated immunoglobulin heavy chain variable region (IGHV) were included in the study. 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 (except for subjects with leukemic infiltration of the liver), 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. The planned dose of BREYANZI was 100 × 106 CAR-positive viable T cells. Bridging therapy for disease control was permitted between apheresis and the start of lymphodepleting chemotherapy.

Of the 89 patients, BREYANZI was administered 2 to 11 days following completion of lymphodepleting chemotherapy. The lymphodepleting chemotherapy regimen consisted of fludarabine 30 mg/m2/day and cyclophosphamide 300 mg/m2/day concurrently for 3 days. BREYANZI was administered in the inpatient (88%) and outpatient (12%) settings.

Of 113 patients who underwent leukapheresis, 94 received BREYANZI. Of the 94, 84 received BREYANZI at 90 to 111 × 106 CAR-positive T cells and 10 received a cell-dose outside of this dose range; 3 received CAR-positive T cells that did not meet the product specifications for BREYANZI (manufacturing failure); and 16 other patients did not receive BREYANZI for other reasons.

The median time from leukapheresis to product availability was 24 days (range: 19 to 84 days), and the median time from leukapheresis to product infusion was 36 days (range: 28 to 384 days). Of the 89 patients treated with BREYANZI, 69 (78%) received bridging therapy.

Patients had measurable disease present before BREYANZI administration based on IRC assessment. Nineteen of 84 patients were not evaluable for efficacy (13 patients did not have baseline disease assessments performed after completion of bridging therapy, 1 patient lacked measurable disease, and 5 had Richter’s transformation). Of the 65 efficacy-evaluable patients, the median age was 66 years (range: 49 to 82 years), 68% were male, 80% were White, 3% were Black, 1% were Asian. Two-percent were Hispanic and 89% were non-Hispanic. Eighty-three percent of patients had at least one high risk genetic attribute including 43% del(17p), 45% TP53 mutation, 45% unmutated IGHV, and 62% with complex karyotype. Fifty-one percent of the patients had bulky

disease. The median number of prior therapies was 5 (range: 2 to 12). All 65 patients were exposed to a BTK inhibitor, of which 88% were refractory, 1.5% were relapsed, and 11% were intolerant. Of 65 patients who received a BCL-2 inhibitor, 92% were refractory, none relapsed, and 6% were intolerant. A total of 83% had disease refractory to last therapy.

Efficacy was based on overall response rate (ORR) (including complete response [CR] and partial response [PR]) and duration of response (DOR) as determined by an independent review committee (IRC) using 2018 International Workshop CLL (iwCLL) criteria (Tables 17 and 18). The median time to first response (CR or PR) was 1.1 months (range: 0.8 to 17.4 months). The median time to first CR was 3.0 months (range 1.1 to 17.9 months).

Table 17: Response Rate in Relapsed or Refractory CLL/SLL (TRANSCEND-CLL Study)

Outcome	**BREYANZI Treated (N=65)**	**All Leukapheresed Patients (N=113)**
Overall Response Rate[a], n (%)	29 (45)	42 (37)
[95% CI][b]	[32.3, 57.5]	[28.3, 46.8]
Complete Response[a], n (%)	13 (20)	16 (14)
[95% CI][b]	[11.1, 31.8]	[8.3, 22.0]
Partial Response[a], n (%)	16 (25)	26 (23)
[95% CI][b]	[14.8, 36.9]	[15.6, 31.9]

CI=confidence interval; iwCLL=international workshop on chronic lymphocytic leukemia; IRC=independent review committee.

a Per the 2018 iwCLL criteria, as assessed by IRC.

b 2-sided 95% exact Clopper-Pearson CIs .

Table 18: Duration of Response in the TRANSCEND-CLL Study

	BREYANZI-Treated N=65
Number of Responders	**29**
Duration of Response (DOR)[a] (months)	
Median [95% CI]b	35.3 [12.4, NR]
Range	2.0^{+}, 35.3
DOR if Best Response is CR[a](months)	**N=13**
Median [95% CI][b]	NR [15.0, NR]
Range	2.0^{+}, 30.0^{+}
Rate at 12 months (%) [95% CI][b]	100 [NR, NR]
Rate at 18 months (%) [95% CI][b]	87.5 [38.7, 98.1]
DOR if Best response is PR[a](months)	**N=16**
Median [95% CI][b]	12.4 [8.9, NR]

Range	4.1, 35.3
Rate at 12 months (%) [95% CI][b]	60.3 [32.0, 79.8]
Rate at 18 months (%) [95% CI][b]	46.9 [21.4, 68.9]

CI=confidence interval; NR=not reached.

[a] Per the 2018 iwCLL criteria, as assessed by IRC.

[b] Kaplan-Meier method was used to obtain 2-sided 95% CIs.

[+]Indicates a censored value.

Minimal residual disease (MRD) negative status was defined as less than one CLL cell per 104 leukocytes using ClonoSEQ, a next generation sequencing assay (NGS) at any time post infusion (MRD-negativity rate). There was no statistical testing of MRD-negativity rate. In patients who achieved CR, the MRD-negativity rate was 100% (13/13, 95% CI: 75.3, 100) in peripheral blood and 92.3% (12/13, 95%CI: 64, 99.8) in the bone marrow.

15 REFERENCES

1. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014;124:188-195.

16 HOW SUPPLIED/STORAGE AND HANDLING

BREYANZI consists of genetically modified autologous T cells, supplied in vials as separate frozen suspensions of each CD8 component (NDC 73153-901-08) and CD4 component (NDC 73153-902-04). Each CD8 or CD4 component is packed in a carton containing up to 4 vials, depending upon the concentration of the cryopreserved drug product CAR-positive viable T cells. The cartons for each CD8 component and CD4 component are in an outer carton (NDC 73153-900-01). BREYANZI is shipped directly to the cell lab or clinical pharmacy associated with the infusion center in the vapor phase of a liquid nitrogen shipper. A Release for Infusion (RFI) Certificate for each component and patient-specific syringe labels are affixed inside the shipper.

- Confirm patient identity upon receipt.
- Store vials in the vapor phase of liquid nitrogen (less than or equal to minus 130°C) in a temperature-monitored system.
- Thaw BREYANZI prior to infusion *[see Dosage and Administration (2.2)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Ensure that patients understand the risk (11%) of manufacturing failure. In case of a manufacturing failure, a second manufacturing of BREYANZI may be attempted. While the patient awaits the product, additional bridging therapy (not the lymphodepletion) may be necessary. This bridging therapy may be associated with adverse events during the pre-infusion period, which could delay or prevent the administration of BREYANZI.

Advise patients that they will be monitored daily for at least 7 days following the BREYANZI infusion at a REMS-certified healthcare facility and instruct patients to remain

within 2 hours of a REMS-certified healthcare facility for at least 4 weeks following the infusion.

Prior to infusion, advise patients of the following risks:

- Cytokine Release Syndrome (CRS) – Signs and symptoms of CRS (fever, chills, hypotension, tachycardia, hypoxia, and fatigue). Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].*
- Neurologic Toxicities – Signs or symptoms associated with neurologic events including encephalopathy, confusion, decreased consciousness, speech disorders, tremor, and seizures. Counsel patients to seek immediate medical attention should signs or symptoms of neurologic toxicity occur at any time *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)].*
- Serious Infections – Signs or symptoms associated with infection *[see Warnings and Precautions (5.5) and Adverse Reactions (6.1)]*.
- Prolonged Cytopenias – Signs or symptoms associated with bone marrow suppression including neutropenia, anemia, thrombocytopenia, or febrile neutropenia *[see Warnings and Precautions (5.6) and Adverse Reactions (6.1)].*
- Secondary Malignancies: Secondary malignancies, including T cell malignancies, have occurred *[see Boxed Warning, Warnings and Precautions (5.8), Adverse Reactions (6.3)].*

Advise patients of the need to:

- Contact Bristol-Myers Squibb at 1-888-805-4555 if they are diagnosed with a secondary malignancy *[see Warnings and Precautions (5.8)]*.
- Refrain from driving or operating heavy or potentially dangerous machines until at least 8 weeks after BREYANZI administration *[see Warnings and Precautions (5.9)].*

Manufactured by:

Juno Therapeutics Inc., a Bristol-Myers Squibb Company, Bothell, WA 98021. US License No.: 2156.

Celgene Corporation, a Bristol-Myers Squibb Company, Summit, NJ 07901. US License No.: 2252.

Bristol-Myers Squibb Company, Devens, MA 01434. US License No.: 1713.

BREYANZI® is a trademark of Juno Therapeutics, Inc., a Bristol-Myers Squibb Company.

Pat. https://www.bms.com/patient-and-caregivers/our-medicines.html

BREPI.006/MG.005

MEDICATION GUIDE
BREYANZI® (pronounced braye an' zee)
(lisocabtagene maraleucel)

Read this Medication Guide before you start your BREYANZI treatment. The more you know about your treatment, the more active you can be in your care. Talk with your healthcare provider if you have questions about your health condition or treatment. Reading this Medication Guide does not take the place of talking with your healthcare

provider about your treatment.

What is the most important information I should know about BREYANZI?

BREYANZI may cause side effects that are life-threatening and can lead to death. Call your healthcare provider or get emergency help right away if you get any of the following:

- difficulty breathing
- fever (100.4°F/38°C or higher)
- chills/shaking chills
- confusion
- severe nausea, vomiting, diarrhea
- fast or irregular heartbeat
- dizziness/lightheadedness
- severe fatigue or weakness

It is important that you tell your healthcare providers that you have received BREYANZI and to show them your BREYANZI Patient Wallet Card. Your healthcare provider may give you other medicines to treat your side effects.

What is BREYANZI?

BREYANZI is a prescription medicine used to treat two types of non-Hodgkin lymphoma:

- Large B cell lymphoma, when:
    - your first treatment has not worked or your cancer returned within a year of your first treatment OR
    - your first treatment has not worked or your cancer returned after the first treatment, and you are not eligible for hematopoietic stem cell transplantation because of medical conditions or age OR
    - two or more kinds of treatment have not worked or stopped working.
- Chronic lymphocytic leukemia or small lymphocytic lymphoma when two or more kinds of treatment have not worked or stopped working.

BREYANZI is different than other cancer medicines because it is made from your own white blood cells, which have been genetically modified to recognize and attack your lymphoma cells.

Before getting BREYANZI, tell your healthcare provider about all your medical problems, including if you have or have had:

- Neurologic problems (such as seizures, stroke, or memory loss)
- Lung or breathing problems
- Heart problems
- Liver problems
- Kidney problems
- A recent or active infection

Tell your healthcare provider about all the medications you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive BREYANZI?

- BREYANZI is made from your own white blood cells, so your blood will be collected

by a process called “leukapheresis” (LOO-kuh-feh-REE-sis).
- It takes about 3-4 weeks from the time your cells are received at the manufacturing site and are available to be shipped back to your healthcare provider, but the time may vary.
- Before you get BREYANZI, you will get 3 days of chemotherapy to prepare your body.
- When your BREYANZI is ready, your healthcare provider will give it to you through a catheter (tube) placed into your vein (intravenous infusion). BREYANZI is given as infusions of 2 different cell types.
    - You will receive infusions of one cell type, immediately followed by the other cell type.
    - The time for infusion will vary but will usually be less than 15 minutes for each of the 2 cell types.
- During the first week, you will be monitored daily by the facility where you received your treatment.
- You should plan to stay within 2 hours of the location where you received your treatment for at least 4 weeks after getting BREYANZI. Your healthcare provider will check to see that your treatment is working and help you with any side effects that may occur.
- You may be hospitalized for side effects and your healthcare provider will discharge you if your side effects are under control, and it is safe for you to leave the hospital.
- Your healthcare provider will want to do blood tests to follow your progress. It is important that you do have your blood tested. If you miss an appointment, call your healthcare provider as soon as possible to reschedule.

What should I avoid after receiving BREYANZI?

- Do not drive, operate heavy machinery, or do other activities that could be dangerous if you are not mentally alert, for at least 8 weeks after you get BREYANZI. This is because the treatment can cause temporary memory and coordination problems, including sleepiness, confusion, dizziness, and seizures.
- Do not donate blood, organs, tissues, or cells for transplantation.

What are the possible or reasonably likely side effects of BREYANZI?

The most common side effects of BREYANZI are:

- fatigue
- difficulty breathing
- fever (100.4°F/38°C or higher)
- chills/shaking chills
- confusion
- difficulty speaking or slurred speech
- severe nausea, vomiting, diarrhea
- headache
- dizziness/lightheadedness
- fast or irregular heartbeat
- swelling

BREYANZI can increase the risk of life-threatening infections that may lead to death. Tell your healthcare provider right away if you develop fever, chills, or any signs or symptoms of an infection.
BREYANZI can lower one or more types of your blood cells (red blood cells, white blood cells, or platelets). After treatment, your healthcare provider will test your blood to check for this. Tell your healthcare provider right away if you get a fever, are feeling tired, or have bruising or bleeding.
BREYANZI may increase your risk of getting cancers including certain types of blood cancers. Your healthcare provider should monitor you for this.
Having BREYANZI in your blood may cause a false-positive HIV test result by some commercial tests.
These are not all the possible side effects of BREYANZI. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of BREYANZI

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about BREYANZI, talk with your healthcare provider. You can ask your healthcare provider for information about BREYANZI that is written for health professionals.
For more information, go to BREYANZI.com or call 1-888-805-4555.
Manufactured by:
Juno Therapeutics Inc., a Bristol-Myers Squibb Company, Bothell, WA 98021. US License No.: 2156.
Celgene Corporation, a Bristol-Myers Squibb Company, Summit, NJ 07901. US License No.: 2252.
Bristol-Myers Squibb Company, Devens, MA 01434. US License No.: 1713.
BREYANZI® is a trademark of Juno Therapeutics, Inc., a Bristol-Myers Squibb Company.
Pat. https://www.bms.com/patient-and-caregivers/our-medicines.html
BREMG.005 03/2024

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Revised: March 2024

PRINCIPAL DISPLAY PANEL - Kit Carton

lisocabtagene maraleucel
Breyanzi™

lisocabtagene maraleucel
Breyanzi®

NDC 73153-900-01
Rx only

FOR AUTOLOGOUS & INTRAVENOUS USE ONLY

Dispense with Medication Guide

Dosage: See Release for Infusion Certificate (inside shipper).

Contains DMSO 7.5% v/v.

1 to 4 single-dose vials/component. Each vial
contains up to 70 x 10^6 CAR-positive viable T cells/mL.
4.6 mL per vial.

Store at ≤ -130°C; vapor phase of liquid nitrogen.
Do not filter or irradiate.
Not evaluated for infectious substances.
Discard unused portion.

Manufactured by:
Juno Therapeutics, Inc., a Bristol-Myers Squibb Company
Bothell, WA 98021
Phone: 1-888-805-4555
US License #: 2156

304029

NDC 73153-900-01

VERIFY
PATIENT
ID

First: FIRST NAME
Last: LAST NAME
Date of birth: DD-MMM-YYYY
JOIN: XXXX-XXXXX
Aph ID/DIN: XXX XXX XXX XXX

CD8
component

CD4
component

Lot
XXXX-XXXXXY
XXXX-XXXXXY

Expiration
DD-MMM-YYYY
DD-MMM-YYYY

STOP
Confirm patient ID
prior to infusion

BREYANZI

lisocabtagene maraleucel kit

Product Information			
Product Type	CELLULAR THERAPY	**Item Code (Source)**	NDC:73153-900

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:73153-900-01	1 in 1 CARTON; Type 0: Not a Combination Product		

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1 VIAL, SINGLE-DOSE	5 mL
Part 2	1 VIAL, SINGLE-DOSE	5 mL

Part 1 of 2

BREYANZI (CD4)

lisocabtagene maraleucel injection, suspension

Product Information	
Item Code (Source)	NDC:73153-902
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LISOCABTAGENE MARALEUCEL (UNII: 7K2YOJ14X0) (LISOCABTAGENE MARALEUCEL - UNII:7K2YOJ14X0)	LISOCABTAGENE MARALEUCEL	50000000 in 5 mL

Inactive Ingredients	
Ingredient Name	**Strength**
DIMETHYL SULFOXIDE (UNII: YOW8V9698H)	
ALBUMIN HUMAN (UNII: ZIF514RVZR)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:73153-902-04	5 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125714	02/05/2021	

Part 2 of 2

BREYANZI (CD8)

lisocabtagene maraleucel injection, suspension

Product Information	
Item Code (Source)	NDC:73153-901
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LISOCABTAGENE MARALEUCEL (UNII: 7K2YOJ14X0) (LISOCABTAGENE MARALEUCEL - UNII:7K2YOJ14X0)	LISOCABTAGENE MARALEUCEL	50000000 in 5 mL

Inactive Ingredients	
Ingredient Name	**Strength**
DIMETHYL SULFOXIDE (UNII: YOW8V9698H)	
ALBUMIN HUMAN (UNII: ZIF514RVZR)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:73153-901-08	5 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125714	02/05/2021	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125714	02/05/2021	

Labeler - Juno Therapeutics, Inc. (079290042)

Revised: 3/2024 Juno Therapeutics, Inc.