

**Division Director Memo**  
**Division of Clinical Evaluation and Pharmacology/Toxicology**  
**Office of Tissues and Advanced Therapies**

<b>APPLICATION:</b> BLA 125714	<b>TRADE NAME:</b> BREYANZI
<b>APPLICANT/SPONSOR:</b> Juno Therapeutics, Inc.	<b>ESTABLISHED NAME:</b> Lisocabtagene maraleucel (JCAR017)
<b>SUBMISSION DATE:</b> 12/18/2019	
<b>PDUFA DATE:</b> 11/16/2020	<b>PRODUCT CLASS:</b> CD19- directed, genetically modified autologous T cell immunotherapy
<b>REVIEW DATE:</b> 11/13/2020	<b>ROUTE:</b> Intravenous infusion

**INDICATION:** Treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least two or more lines of systemic therapy, 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

**Review Team** (for comprehensive review team members from other offices, please see SBRA)

**Clinical:** Drs. Megha Kaushal, Kavita Natrajan and Yvette Kasamon (OCE); **Statistical:** Dr. Cong Wang; **Pharm/Tox:** Dr. Christopher Saeui; **Clin Pharm:** Dr. Xiaofei Wang; **CMC:** Drs. Kimberly Shultz, Nirjal Bhattarai, and Tiffany Lucas

**REVIEW SUMMARY:**

Juno Therapeutics, Inc. submitted this original BLA to seek marketing approval for BREYANZI, a CD19- directed, genetically modified autologous T cell immunotherapy, for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least two or more lines of systemic therapy.

The primary evidence of safety and efficacy to support this application comes from the Diffuse Large B-Cell Lymphoma (DLBCL) cohort from Study 017001 (TRANSCEND), a single-arm, open-label and multicenter study in adults with relapsed or refractory (R/R), de novo or transformed large B-cell non-Hodgkin lymphoma (NHL) after two or more lines of systemic therapy. The DLBCL cohort enrolled 344 subjects with DLBCL de novo, transformed follicular lymphoma (tFL), high-grade B-cell lymphoma (HGL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma Grade 3B (FL3B). Of the 344 subjects who underwent leukapheresis, 269 were treated with BREYANZI and 256 of the 269 treated subjects were considered efficacy-evaluable and comprised the primary efficacy analysis set. The pre-specified primary efficacy endpoint was overall response rate (ORR), defined as the proportion of subjects with a best overall response (BOR) of either complete response (CR) or partial response (PR), as assessed by the Independent Review Committee (IRC)-FDA algorithm. Key secondary efficacy endpoints included duration of response (DOR), CR, PR, progression-free survival (PFS), and overall survival (OS).

The ORR as assessed by the IRC-FDA algorithm was 71.5% (183/256; 95% CI: 65.5%, 76.9%), and BOR of CR was 53.1% and PR was 18.4%. The median duration of response (DOR) for: 1) all subjects was 16.7 months (95% CI: 6.0, NR) for all responders with a median follow-up time of 12.9 months (95% CI: 11.3, 17.0), 2) for complete responders, was not reached yet as of the data cut-off date (95% CI: 16.8, NR) and 3) for the partial responders was 2.0 months (95% CI: 1.2, 2.4). The median PFS was 3.5 months (95% CI: 3.0, 8.8) with a median follow-up time of 12.8 months (12.1, 17.7) and the median OS was 21.1 months (95% CI: 13.3, NR) with a median follow-up time of 17.5 months (95% CI: 13.2, 17.9). Although a few different dosing regimens were evaluated, the majority of efficacy-evaluable subjects (192/256; 75%) received the study drug as a single dose of  $50$  to  $110 \times 10^6$  CAR+ viable T cells (recommended dose), in whom the ORR [73.4% (95% CI: 66.6%, 79.5%)] and CR [54.2% (95% CI: 46.8%, 61.4%)] were similar to the DLBCL full efficacy analysis set.

With respect to safety, serious adverse reactions associated with BREYANZI included cytokine release syndrome, neurologic toxicity, prolonged cytopenias, infections, and hypogammaglobulinemia. Cytokine release syndrome (CRS) and neurologic toxicity were reported in 46% and 35% of subjects, respectively. Grade 3 and higher CRS and neurotoxicity were reported in 4% and 12% of subjects, respectively. Other common adverse reactions occurring at an incidence of  $\geq 20\%$ , included fatigue, nausea, headache, decreased appetite, diarrhea, hypotension, tachycardia, dizziness, cough, constipation, infections (pathogen unspecified), abdominal pain, and vomiting. Fatal cases of CRS and neurologic toxicity have occurred in a small number of subjects.

**Division Director Memo**  
**Division of Clinical Evaluation and Pharmacology/Toxicology**  
**Office of Tissues and Advanced Therapies**

<b>APPLICATION:</b>	BLA 125714	<b>TRADE NAME:</b>	BREYANZI
<b>APPLICANT/SPONSOR:</b>	Juno Therapeutics, Inc.	<b>ESTABLISHED NAME:</b>	Lisocabtagene maraleucel (JCAR017)
<b>SUBMISSION DATE</b>	12/18/2019		
<b>PDUFA DATE</b>	11/16/2020	<b>PRODUCT CLASS:</b>	CD19- directed, genetically modified autologous T cell immunotherapy
<b>REVIEW DATE:</b>	11/13/2020	<b>ROUTE:</b>	Intravenous infusion

Additionally, there were very limited data in subjects with CNS disease that precluded any assessment of treatment effect, particularly due to small number of subjects and confounding factors; however, BREYANZI appeared to be safe in the seven subjects who received targeted bridging therapy without an increased risk of CNS toxicity.

I conclude that the Applicant has provided substantial evidence of effectiveness and safety from an adequate and well controlled study for the proposed indication as well as confirmatory evidence from nonclinical studies, and that the benefit/risk profile is favorable with implementation of a REMS for the serious life-threatening risks of CRS and neurotoxicity. I concur with the review team's, to include OCE's, recommendation of Approval with a Risk Mitigation and Evaluation Strategy (REMS) and a PMR for a postmarketing observational study to assess long-term toxicities of BREYANZI, particularly secondary malignancies.

**OUTSTANDING ISSUES:**

Although there are no pharmacology/toxicology, clinical pharmacology, or clinical issues that would preclude approval, there is a pre-approval licensure inspection of the vector manufacturing facility that is pending at this time.

**RECOMMENDED REGULATORY ACTION**

**APPROVAL**
                         
  **COMPLETE RESPONSE**

Tejashri Purohit-Sheth, M.D.  
 Director  
 Division of Clinical Evaluation and Pharmacology/Toxicology  
 Office of Tissues and Advanced Therapies  
 Center for Biologics Evaluation and Research  
 U.S. Food and Drug Administration