

## BLA Clinical Review Memorandum Addendum

<b>Application Type</b>	Original BLA
<b>STN</b>	125714/0
<b>CBER Received Date</b>	December 18, 2019
<b>PDUFA Goal Date</b>	November 16, 2020
<b>Division / Office</b>	DCEPT/OTAT DHM II/OCE
<b>Priority Review (Yes/No)</b>	Yes
<b>Reviewer Name(s)</b>	Megha Kaushal, MD (Efficacy) Kavita Natrajan, MD (Safety)
<b>Review Completion Date / Stamped Date</b>	11/13/2020 Addendum on 2/3/2021
<b>Supervisory Concurrence</b>	Yvette Kasamon, MD Bindu George, MD Marc Theoret, MD
<b>Applicant</b>	Juno Therapeutics
<b>Established Name</b>	Lisocabtagene maraleucel (JCAR017)
<b>(Proposed) Trade Name</b>	BREYANZI
<b>Pharmacologic Class</b>	CD19- directed, genetically modified autologous T cell immunotherapy
<b>Formulation(s), including Adjuvants, etc.</b>	75% Cryostor® CS10 [containing 7.5% dimethylsulfoxide], 24% Multiple Electrolytes for Injection, Type 1, 1% of 25% albumin (human)
<b>Dosage Form(s) and Route(s) of Administration</b>	Intravenous
<b>Dosing Regimen</b>	Single dose containing 50 to 110 x10 <sup>6</sup> CAR-positive viable T cells (consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components) by IV infusion and preceded by fludarabine and cyclophosphamide chemotherapy for lymphodepletion
<b>Indication(s) and Intended Population(s)</b>	<u>Proposed</u> : Treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies. <u>Limitation of Use</u> : Not indicated for the treatment of patients with primary central nervous system lymphoma

	<p><u>Recommended:</u> Treatment of adult patients with relapsed or refractory large B-cell lymphoma, after 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.</p> <p><u>Limitations of use:</u> Not indicated for the treatment of patients with primary central nervous system lymphoma.</p>
<b>Orphan Designated (Yes/No)</b>	Yes

## Addendum to Clinical Review Memo:

Labeling negotiations continued after the completion of the clinical review memo. During this time, revisions to the label included clarification to the leukapheresed population in Section 14 (efficacy). As stated in the review memo, 344 subjects were leukapheresed which included subjects intended to receive DL1, DL2, and DL3. In the label, it was agreed that the Applicant would only include subjects in the leukapheresed population intended to receive DL1 and DL2, as these were the dose levels subjects received for the approved dose range of 50-110 x 10<sup>6</sup> CAR+ T cells.

This population includes 299 subjects leukapheresed, where

- 204 subjects were administered BREYANZI in the approved dose range of 50-110 x 10<sup>6</sup> CAR+ T cells, of whom 192 had radiographically evaluable disease prior to the infusion and comprise the main efficacy-evaluable population
- 44 subjects were assigned to a dose level but not treated
- 26 subjects received BREYANZI outside of the approved dose range and 25 subjects were infused with investigational product that did not meet release specifications. See table below.

Patients in Leukapheresed Set - DL1 and DL2 only (299)	Responders
Administered BREYANZI in the approved dose range (204) <sup>a</sup>	148
Assigned to a dose but not treated (44)	0
Administered BREYANZI outside of the approved dose range (26)	14
Infused with investigational product that did not meet release specifications (25)	13

<sup>a</sup> Includes 12 patients with radiographically inevaluable disease

Although there were additional subjects who had a response in this leukapheresed population, the clinical team recommended that only the responses of subjects who received the recommended dose and were efficacy evaluable should be included in the PI. This would exclude the additional 34 responses from those who were not efficacy evaluable, received product outside the dose range, and those who received out of specification product. The clinical team agreed that there would be little relevance to prescribers discussing responses related to a non-approved dose or product. This was further discussed during a telecon with the Applicant. The Applicant agreed to remove these responses from the table in the PI, but added a footnote detailing the responses to this leukapheresed population. The clinical team did not agree to this change where there was an implied efficacy claim for the product and doses outside the recommended dose range or product not meeting release specifications.

The clinical team met with the OTAT director and signatory authority for this application to relay the clinical teams' concerns of whether the leukapheresed population should be included in the table, and if so, whether the response rates should be included as a footnote to the table in the PI. The OTAT director recommended the following:

- 1) Narrative text for the leukapheresed population with details of the populations included
- 2) Inclusion of the responses incorporated for the ORR, CR, and PR rate in the leukapheresed population
- 3) Consideration of exclusion of subjects who were not efficacy evaluable from the leukapheresed population

Therefore, the final PI included a narrative for the leukapheresed population (299 subjects). This included the 44 subjects who did not receive the product, 204 subjects who received the product in the approved dose range, and 51 subjects who received the product outside the recommended dose range or received product did not meet product specification. The narrative further stated of those leukapheresed with evaluable disease (287 subjects), the ORR 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). Efficacy in the leukapheresed population was only included as text and not in tabular format.

The Applicant agreed to these changes.