



Our STN: BLA 125714/0

**LATE-CYCLE
MEETING MEMORANDUM**
October 1, 2020

Juno Therapeutics, Inc.
Attention: Joy Seymour
400 Dexter Avenue North
Suite 1200
Seattle, WA 98109

Dear Ms. Seymour:

Attached is a copy of the memorandum summarizing your September 2, 2020 Late-Cycle Meeting [teleconference] with CBER. This memorandum constitutes the official record of the teleconference. If your understanding of the teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (BLA 125714) in future submissions related to the subject product.

If you have any questions, please contact Zakaria Ganiyu at (240) 402 – 8329.

Sincerely,

Raj Puri, PhD
Director
Division of Cellular and Gene Therapies
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

Late-Cycle Meeting Summary

Meeting Date and Time: September 2, 2020 at 12:20PM - 2:00PM, EDT
Meeting Location: Via WebEx (Teleconference)
Application Number: 125714/0
Product Name: lisocabtagene maraleucel
Indication: Treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies.
Applicant Name: Juno Therapeutics,
Meeting Chair: Kimberly Schultz, PhD
RPM: Zakaria Ganiyu, MS, MBA

FDA ATTENDEES

Rachael Anatol, PhD, CBER/OTAT
Marie Anderson, PhD, CBER/OCBQ/DBSQC
Rabia Ballica, PhD, CBER/OCBQ/DMPQ
Kimberly Benton, PhD, CBER/OTAT
Nirjal Bhattarai, PhD CBER/OTAT/DCGT
Wilson Bryan, MD, CBER/OTAT
Nannette Cagungun, MS, PD, RAC, CBER/OTAT/DRPM
Christine Drabick, OCBQ/BIMO
Oluchi Elekwachi, PharmD, MPH, CBER
John Eltermann, RPh, MS, CBER/OCBQ/DMPQ
Zakaria Ganiyu, MS, MBA, CBER/OTAT/DRPM
Denise Gavin, PhD, CBER/OTAT/DCGT
Andrew Harmon, PhD, CBER/OTAT/DCGT
Yvette Kasamon, MD, CDER/OND
Megha Kaushal, MD, CBER/OTAT/DCEPT
Niloofer Kennedy CBER/OTAT/DRPM
Hyesuk Kong, PhD, CBER/OCBQ/DBSQC
Wei Liang, PhD, CBER/OTAT
Tiffany Lucas, PhD, CBER/OTAT/DCGT
Darya Melnyk, PhD, CBER/OCBQ/DBSQC
Nair Narayan, MD, CBER/OBE
Kavita Natrajan, MD, CBER/OTAT/DCEPT
Steven Oh, PhD, CBER/OTAT/DCGT
Raj Puri, MD, PhD, CBER/OTAT/DCGT
Tejashri Purohit-Sheth, MD, CBER/OTAT/DCEPT
Carolyn Renshaw, CBER/OCBQ/DMPQ
Christopher Saeui, PhD, CBER/OTAT/DCEPT
Kimberly Schultz, PhD, CBER/OTAT/DCGT
Ramani Sista, PhD, CBER/OTAT/DRPM
Lisa Stockbridge, PhD, CBER/OCBQ/DCM/APLB
Deborah Thompson, MD, MSPH, CBER/OBE/DE
Lori Tull, CBER/OTAT/DRPM

Ramjay Vatsan, PhD, CBER/OTAT/DCGT
Cong Wang, PhD, CBER/OBE/DB
Xiaofei Wang, PhD, CBER/OTAT/DCEPT
Yuan Xu, CDER/OTS/OCP/DPM
Zhenzhen Xu, PhD, CBER/OBE/DB

APPLICANT ATTENDEES

Maria Brown, Cell Therapy Development & Operations	Daniel Li, Biostatistics	John Pribble, Global Drug Development
Wendy Corbett, Global Regulatory Sciences	Yeonhee Kim, Biostatistics	(b) (6), Global Labeling
Christine Dehner, Global Drug Development	Candace Larson, Project Leadership	Joycelyn Seymour, Global Regulatory Sciences
Jennifer Dudinak, Global Regulatory Sciences	Ann Lee, Cell Therapy Development & Operations	Annie Sturgess, Global Regulatory Sciences-CMC
Melanie Eatough, Global Labeling	Duyen Mai, Global Risk Management	Wayne Wallis, Global Drug Safety
David Fontana, Project Leadership	Mary Mallaney, CMC	(b) (6) CMC
Stanley Frankel, Global Drug Development	Candice McCoy, Global Drug Development	Cheryl Watson, Global Regulatory Sciences-CMC
Mathias Hukkelhoven, Global Regulatory Sciences	Feisal Othman, Global Risk Management	Ferdinando Vegni, Global Drug Safety
Ana Kostic, Global Drug Development	Stefano Pozzi, Global Medical Affairs	Krishan Viswanadhan, Project Leadership
(b) (6), Global Drug Development	Patricia Pretara, Global Regulatory Sciences	Roelf Zondag, Global Development Operations

BACKGROUND

BLA 125714/0 was submitted on December 18, 2019 for lisocabtagene maraleucel (BREYANZI)

Proposed indications: Treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies.

PDUFA Goal Date: November 16, 2020

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on August 21, 2020.

MEETING DISCUSSION

Facility Inspections

FDA confirmed that inspections of the Juno Therapeutics Inc. (FEI# 3011834594, Bothell, WA) and (b) (4) facilities are required before the application can be approved. The Applicant requested Agency confirmation that the pre-approval inspections noted above are considered to be “mission critical” by FDA given that lisocabtagene maraleucel (liso-cel) has received BTD and addresses a patient population of unmet medical need. FDA stated that internal discussion is ongoing on the determination of these inspections as “mission critical”. The Applicant sought input on potential hybrid approaches to completing on-site inspections as outlined in the pre-read slides. The Agency noted that it is actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors. FDA stated that they are still actively reviewing the pre-inspection documents previously submitted to the BLA (SN0053, dated 19 June 2020 and SN0055, dated 29 June 2020) and expect to issue an information request (IR) related to these documents during the following week. FDA indicated that they would inform the Applicant of any decision on deferred action or a complete response letter by the action due date of 16 November 2020.

Advisory Committee Meeting

FDA confirmed in the LCM materials that an Advisory Committee Meeting is not planned. There was no further discussion during the meeting.

Risk Management and REMS

FDA confirmed in the LCM materials that a REMS is necessary and noted that Agency review is ongoing for the proposed REMS program. The Applicant confirmed that the outstanding response to IR #68 on REMS will be submitted to the BLA by the requested due date of 11 September 2020.

Ongoing Stability Data Update

In the LCM materials, FDA noted their agreement to accept an ongoing stability data update within 60 days prior to the PDUFA date. The Applicant previously indicated that the target date for the submission is no later than 17 September 2020 and the Agency recommended submission of this information for review as soon as possible, especially given that this agreement was made without consideration for the major amendment. The Applicant acknowledged FDA’s recommendation and confirmed that the stability update will be submitted via email by 04 September 2020 and as a BLA amendment by 10 September 2020.

Submission of Updated Module 3 Sections to BLA After Commercial Release Criteria are Final

In the LCM materials, FDA noted that commercial lot release acceptance criteria are still under negotiation. The Agency requested an update of the lot release table in BLA in sections 3.2.S.4.1 (b) (4) and 3.2. P.5.1 (lisocabtagene maraleucel) after the commercial lot release criteria negotiations are complete. The Applicant acknowledged the Agency’s comments and clarified that:

- a. updates to Module 3 sections are planned to be submitted as BLA amendments in real-time, as release criteria are finalized, and
- b. a reviewers guide will be included to provide details and rationale on the revisions made within each section.

The Applicant noted their understanding that the (b) (4) specification is final and indicated that a submission with a revised S.4.1 section will be included in a BLA amendment. The Agency acknowledged the Applicant's comment.

INFORMATION REQUESTS DISCUSSED DURING THE MEETING

IR #68 – REMS

The Applicant confirmed that the outstanding response to IR #68 on REMS will be submitted to the BLA by the requested due date of 11 September 2020.

IR #69, FDA Comment 1 – Dose and Strength Release Criteria

The Applicant presented the information for IR #69 Comment 1 included in the Applicant's pre-read slides.

There was additional discussion on the dose range, target dose, and the potential to revise cell viability acceptance criteria, summarized below:

- a. FDA confirmed that the efficacy evaluable population used as the basis for the dose response assessment included the full range of experience across drug product manufacturing using process versions (b) (4)
- b. The Agency stated that for Study 017001, the small sample size below the FDA determined dose range of 50×10^6 CAR+ viable T cells and the short follow up for durability of response above 110×10^6 were insufficient to establish efficacy.
- c. The Agency noted that a clinical justification for the target dose of 100×10^6 CAR+ viable T cells is required.
- d. FDA confirmed that the previously agreed cell viability acceptance criteria specification based solely on process version (b) (4) is final and data from process versions (b) (4) will not be considered.
- e. FDA further confirmed that in the US Prescribing Information (PI), the data cutoff date of 12 April 2019 will be used for safety (N=268 treated subjects) and the data cutoff date of 12 August 2019 will be used for efficacy (N=256 efficacy-evaluable subjects).
- f. The Agency was not able to provide an estimate on when they anticipate sending the first draft of the US PI to the Applicant for review but indicated that FDA could follow-up after the meeting.

POSTMARKETING REQUIREMENTS/ POSTMARKETING COMMITMENTS

(b) (4) Validation

In the LCM materials, FDA noted that in BLA amendment 0053, received on 26 June 2020, the Applicant provided a prospective validation protocol for (b) (4). As discussed at the 19 June 2020 teleconference, this assay validation will be conducted as a postmarketing commitment. The Applicant confirmed that in the response to FDA IR #70 dated 25 August 2020, submitted to BLA

125714 on 28 August 2020 (SN0064), the Applicant committed to prospectively validating the (b) (4) per protocol (b) (4) and confirmed that the final study report will be submitted by 30 September 2021.

Postmarketing Registry Study

In the LCM materials, FDA noted that if the application is approved, the Applicant will be required to conduct the following study as a PMR under Section 505(o) of FDCA: A post-marketing, prospective, multi-center, observational study to assess the long-term safety of liso-cel and the risk of all secondary malignancies occurring after treatment with liso-cel. The study will include at least 1000 adult patients with relapsed/refractory large B-cell lymphoma; the enrolled patients will be followed for 15 years after product administration. FDA acknowledged the timetable proposed in the draft protocol for the postmarketing registry study, which includes the following milestones:

- a. Final protocol submission: January 31, 2021
- b. Study completion: Q1 2041
- c. Final study report: Q2 2042

The Agency requested dates in mm/dd/yyyy format for Study Completion and Final Report Submission.

The Applicant confirmed the following dates for the postmarketing registry study:

- a. Study completion 03/31/2041
- b. Final study report 06/30/2042

In response to the Applicant's question included in the LCM pre-read slides, the Agency confirmed that at least 1500 patients will be required to be enrolled and followed for 15 years after liso-cel administration. FDA further confirmed that 500 of the 1500 total patients may be enrolled from liso-cel ongoing and planned interventional clinical trials.

ADDITIONAL APPLICANT QUESTIONS DURING THE MEETING

NDC Codes

The Applicant referred to the proposal for NDC codes submitted in M1-14-1-1 (Draft Carton and Container Labels – summary) BLA 125714, SN0002 on 30 October 2019, and the preliminary FDA agreement on the NDC codes proposal indicated in the Mid-Cycle Communication Summary (dated 17 April 2020). The Applicant requested FDA confirmation that the NDC code proposal is acceptable and no validation issues at the time of SPL submission of final labeling are anticipated. The Agency indicated there was no change to their preliminary feedback, but notification would be provided as soon as possible if their position changed. FDA provided the name of Michael Fauntleroy as a point of contact at FDA with whom the Applicant can work to avoid SPL validation issues.

GCP Inspections for Study 017001

The Applicant noted that two FDA site inspections have been completed with one FDA site inspection ongoing at the time of the LCM and requested confirmation if other site

inspections are planned by the Agency. FDA stated that the Agency does not provide the name or the timing of future inspections.

JCAR017-EAP-001: Expanded Access Protocol for Subjects Receiving Lisocabtagene Maraleucel that is Nonconforming for Commercial Release

The Applicant noted that the original JCAR017-EAP-001, Expanded Access Protocol for Subjects Receiving Lisocabtagene Maraleucel that is Nonconforming for Commercial Release and Protocol Amendment 1 were submitted to the JCAR017 IND 016506. FDA commented that the Agency is actively reviewing the Applicant's questions related to JCAR017-EAP-001 Protocol Amendment 1 and will provide responses in early October.

The Applicant further noted that submission of a Type B meeting request is planned by the end of September 2020 to discuss the strategy for widening of specifications with additional clinical data that would be provided in a future BLA supplement. Information would be included in JCAR017-EAP-001 Protocol Amendment 2. FDA thanked the Applicant for advising of future plans.

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.