

Our STN: BL 125746/0

**LATE-CYCLE  
MEETING MEMORANDUM**

Janssen Biotech, Inc.  
Attention: Nancy Nair, PharmD, MBA  
800/850 Ridgeview Drive  
Horsham, PA 19044

Dear Dr. Nair:

Attached is a copy of the memorandum summarizing your September 20, 2021 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 (STN) in future submissions related to the subject product.

If you have any questions, please contact Nadia Whitt at [nadia.whitt@fda.hhs.gov](mailto:nadia.whitt@fda.hhs.gov) and Rachel Blasdell at [rachel.blasdell@fda.hhs.gov](mailto:rachel.blasdell@fda.hhs.gov).

Sincerely,

Raj K. Puri, MD, 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 20, 2021, 12:00-1:30 PM, EST  
**Meeting Location:** Zoom Teleconference  
**Application Number:** BLA 125746/0  
**Product Name:** ciltacabtagene autoleucel  
**Proposed Indications:** Treatment of adult patients with relapsed or refractory multiple myeloma, who previously received a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 antibody  
**Applicant Name:** Janssen Biotech, Inc.  
**Meeting Chair:** Zhaohui Ye, PhD  
**RPMS:** Nadia Whitt and Rachel Blasdell

### **FDA ATTENDEES**

Meghna Alimchandani, MD, CBER/OBE  
Rachael Anatol, PhD, CBER/OTAT  
David Bailey, CBER/OCBQ/DMPQ  
Kimberly Benton, PhD, CBER/OTAT  
Rachel Blasdell, CBER/OTAT/DRPM  
Wilson W. Bryan, MD, CBER/OTAT  
Nannette Cagungun, MS, PD, RAC, CBER/OTAT/DRPM  
Dennis Cato, CBER/OCBQ/DIS/BMB  
Maitreyi Chattopadhyay, PhD, CBER/OTAT/DCGT  
Haecin Chun, CBER/OCBQ/DIS  
Tianjiao Dai, PhD, CBER/OBE/DB  
John Eltermann, RPh, MS, CBER/OCBQ/DMPQ  
Varsha Garnepudi, PhD, CBER/OCBQ/DBSQC  
Denise Gavin, PhD, CBER/OTAT/DCGT  
Bindu George, MD, CBER/OTAT/DCEPT/CHB  
Dana Jones, CBER/OCBQ/DCM  
Beatrice Kallungal, MS, CBER/OTAT/DRPM  
Bindu Kanapuru, CDER/OND/ODD/DHMII  
Megha Kaushal, MD, CBER/OTAT/DCEPT  
Carolyn Laurencot, PhD, CBER/OTAT/DCGT  
Nicole Li, CBER/OCBQ/DMPQ  
Wei Liang, PhD, CBER/OTAT  
Jing Lin, CBER/OCBQ/DBSQC  
Tiffany Lucas, PhD, CBER/OTAT/DCGT  
Bettina Joi McGraw, MD, CBER/OTAT/DCEPT  
Leyish Minie, MSN, RN, CBER/OTAT/DRPM  
Ernesto Moreira, MD, CBER/OTAT/DCEPT  
Brad Moriyama, PharmD, BCCCP, CDER/OSE/DRM  
Narayan Nair, MD, CBER/OBE/DE  
Kavita Natrajan, MD, CBER/OTAT/DCEPT

Manette Niu, MD, CBER/OBE  
Steven Oh, PhD, CBER/OTAT/DCGT  
Joseph Paradis, CDER/OSE/DRM  
Graeme Price, PhD, CBER/OTAT/DCGT/GTIB  
Raj Puri, MD, PhD, CBER/OTAT/DCGT  
Kanaeko Ravenell, CBER/OCBQ/DIS  
Carolyn Renshaw, CBER/OCBQ/DMPQ  
Kimberly Schultz, PhD, CBER/OTAT/DCGT  
Muhammad Shahabuddin, CBER/OCBQ/DBSQC  
Ramani Sista, PhD, CBER/OTAT/DRPM  
Lisa Stockbridge, PhD, CBER/OCBQ/DCM/APLB  
Melek Sunay, PhD, CBER/OTAT/DCEPT  
Zenobia Taraporewala, PhD, CBER/OTAT/DCGT  
Edward Thompson, CBER/OTAT/DRPM  
Lori Tull, CBER/OTAT/DRPM  
Ramjay Vatsan, PhD, CBER/OTAT/DCGT  
Xiaofei Wang, PhD, CBER/OTAT/DCEPT  
Kerry Welsh, CBER/OBE/DE  
Nadia Whitt, CBER/OTAT/DRPM  
Zhaohui Ye, PhD, CBER/OTAT/DCGT  
Iryna Zubkova, PhD, CBER/OCBQ/DMPQ

#### **APPLICANT ATTENDEES**

Janssen Attendees:

Melissa Calmann, PhD - Dir. CMC Regulatory Affairs  
Cristy Dougherty, PhD - Sr. Dir, CMC Regulatory Affairs  
William Deraedt - Clinical Scientist  
Jenna Goldberg, MD - Global Medical Head  
Xavier Hudson, PharmD - NA Regulatory Scientist  
Carolyn Jackson, MD - Sr. Medical Dir., Clinical  
Claire Li, PhD - Assoc. Scientific Dir., Clinical Pharmacology  
Deepu Madduri, MD - Sr. Medical Dir., Clinical  
Jennifer Marino - Compound Development Team Lead  
Loreta Marquez, MD - Dir. Global Medical Safety  
Erin Lee, RN - Dir. Safety Analysis Scientist  
Nancy V. Nair, PharmD, MBA - NA Regulatory Leader  
Aline de Oliveira, PhD - NA Regulatory Scientist  
Bethany Paxson - VP, NA Regulatory Affairs & Diagnostics – Oncology  
Jordan Schechter, MD - VP, Cellular Therapy  
Jean Xu - Dir. CMC Leader Portfolio Mgmt.  
Joanita Aguiar - Dir. Global Labeling Product Leader  
Tzu-min Yeh, MS - Associate Dir. Biostatistics  
Jennifer Yohrling, PhD - Global Regulatory Leader  
Zhilong Yuan - Dir. Statistics  
Andrew Yazwa - Risk Management Lead  
Sen Zhuang, MD, PhD- VP, Clinical Research & Development

Enrique Zudaire, PhD - Translational Medicine  
Gregory Ursino, MD- Group Medical Director CAR T US Med Affairs  
Lisa Kallenbach, MD, MPA- Medical Director, CAR-T MAF  
Phil Powell, MBA - Assoc Dir Principal Research Scientist, CAR-T MAF  
Vadim Romanov, MD, MPhil, FFPM - Head Medical Affairs CAR-T

Legend Biotech Attendees:

Lida Pacaud, MD - VP, Clinical Development Head  
Yuhong Qiu, PhD - VP, Regulatory Affairs  
Jianxin Ye - Exec. Dir., CMC Regulatory Affairs

## **BACKGROUND**

BLA 125746/0 was submitted on March 31, 2021, for ciltacabtagene autoleucel (CARVYKTI).

Proposed indication: For the treatment of adult patients with relapsed or refractory multiple myeloma, who previously received a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 antibody.

PDUFA goal date: November 29, 2021

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on September 10, 2021.

## DISCUSSION

### 1. Discussion of Substantive Review Issues

#### Chemistry, Manufacturing, and Controls (CMC)

- As communicated to the applicant through Information Request #11 (July 9, 2021) and #20 (August 5, 2021), the proposed commercial (b) (4) assay is unacceptable as a standalone potency assay. As discussed in the teleconference on August 12, 2021, FDA tentatively agreed that the (b) (4) assay might be suitable as an additional/alternate assay but additional information (method description, validation, specification, batch analysis results etc.) will be required. The adequacy and timeliness of amendment submission(s) containing the relevant information could have a significant impact on the BLA review conclusion and/or timeline.
- As communicated to the applicant through Information Request #25 (August 20, 2021), the unvalidated (b) (4) assay is not suitable for use in setting the quantity of (b) (4) used to produce the DP, or a part of the LVV lot release acceptance criteria. As discussed in the teleconference on August 26, 2021, the applicant agreed to have a consistent (b) (4) for DP manufacture. To support the (b) (4) that will be used in product manufacturing, the applicant agreed to calculate and submit (b) (4) data from clinical lots based on the (b) (4). These supporting (b) (4) data have been received in Amendments #37 and #38, which are currently under review.
- Janssen confirmed that the (b) (4) assay validation is ongoing and is progressing as anticipated. Janssen asked if the validation data are submitted in early-mid October as originally planned, will the BLA review timeline be affected. The FDA responded that a determination will be made after receiving the amendment containing the data.

#### Inspections

- The (b) (4) facility record request review is ongoing. The (b) (4) inspections was held (b) (4). A final recommendation is pending at this time.
- Janssen requested an anticipated timeline for receipt of the EIR. The Agency responded that the EIR will be provided after approval of the BLA.

### 2. Information Requests

- DMPQ IR sent September 2, 2021; requested Janssen response by September 17, 2021

- DMPQ IR sent September 9, 2021; requested Janssen response by September 17, 2021
- Clinical IR sent September 10, 2021; requested Janssen response by September 17, 2021
- CMC IR sent September 10, 2021; requested Janssen response by September 20, 2021
- Clinical IR sent September 13, 2021; requested Janssen response by September 17, 2021
- Clinical Pharmacology IR sent September 17, 2021; requested Janssen response by October 5, 2021

### 3. Risk Management Actions (e.g., REMS)

The REMS materials are under review and any comments will be sent in an IR.

### 4. Postmarketing Requirements/Postmarketing Commitments

- We have determined that an analysis of spontaneous post-marketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to identify a serious risk of secondary malignancies associated with use of ciltacabtagene autoleucel. Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess this serious risk. Therefore, should this product be approved, you will be required to conduct the following study as a post-marketing requirement (PMR) under Section 505(o) of FDCA: An observational post-authorization safety study to evaluate the safety of multiple myeloma patients treated with ciltacabtagene autoleucel. The study will include at least 1500 adult patients with relapsed or refractory multiple myeloma who previously received a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody; the enrolled patients will be followed for 15 years after product administration.
- We acknowledge the timetable you proposed in the draft protocol for the post-marketing registry study, which includes the following milestones:

Final protocol submission: January 31, 2022

Study completion: June 30, 2041

Final study report: June 30, 2042

### 5. Major Labeling Issues

We are currently reviewing your response to IR#28 pertaining to minimal residual disease (MRD) assessment in the 68284528MMY2001 trial. We have substantial

concerns regarding the reported 20.6% (20/97 subjects) calibration failure rate, which impact the strength and validity of the MRD results. These review issues may impact the labeling section pertaining to MRD information.

## 6. Review Plans

Currently there is no plan to extend the PDUFA goal date. However, submission(s) of additional information to address the review issues may trigger an extension of the goal date. The final determination will also depend on the outcome of the pre-license inspection.

## 7. Applicant Questions

1. Can the FDA provide any plans on whether a sponsor GCP inspection will occur and the target timeframe?
  - FDA stated that the plans to conduct a sponsor GCP inspection cannot be disclosed.
2. In the Mid-cycle meeting, the Agency had noted that the Target Labeling Date is October 29, 2021. Is the Agency able to comment on whether Janssen should still expect the label on that date or earlier?
  - FDA confirmed that the first draft of labeling will be sent on or before October 29, 2021.
3. During the PAI of the (b) (4) facility, the FDA Inspection team queried Janssen regarding the post approval process and management of Out of Specification (OOS) cilta-cel. Janssen would appreciate the opportunity for a discussion with the Agency to review the Expanded Access Program which will provide access to OOS cilta-cel that meets exceptional release criteria.
  - a. Our hybrid strategy of clinical trial and managed access program ensures every commercial site in the U.S. has an OOS solution prior to commercial activation. Janssen acknowledges the burden of sINDs both on the treatment center and FDA, and there are no proactive plans to include sINDs in the cilta-cel OOS solution
  - b. 68284528MMY4006 Managed Access Program (MAP) (Submitted to IND 18080, SN 382): Assigned to approximately 70% of sites. MAP provides for OOS solution at CAR-T sites and requires a contract at each site. Under the MAP program, all sites are expected to have completed contracting prior to commercial activation, and a sIND under this program is highly unlikely.
  - c. 68284528MMY2005 Clinical Trial (Submitted to IND 18080, SN 393): Assigned to approximately 30% of sites. Site contracting is underway,

however not all sites will have completed contracting by anticipated BLA approval date. At these limited sites, there is the potential for a request for a Single Patient IND.

- d. Janssen is committed to working with sites proactively to prepare for an efficient, less time-consuming process. Janssen will assist treating physicians with Form 3926 guidance/preparation and ensure a site's communication with the FDA is as efficient as possible. Janssen also welcomes Agency guidance on any other proposals to mitigate the burden of a potential sIND.
  - FDA requested the applicant to clarify why a hybrid program i.e., a managed access program (MAP) and a clinical trial is being used for patients to receive OOS product following licensure of JNJ68284528. Applicant clarified that while the intent of both programs is for patients to receive OOS product, the clinical trial program (applicable to ~30% of sites) is for the purpose of collecting detailed efficacy and safety data. FDA stated that, as previously noted in the meeting on August 28, 2020 (CRMTS12720), the purpose of an expanded access program (MAP, clinical trial) is for patients to receive OOS product following drug product licensure and is not meant to study safety and efficacy of an investigational (OOS) product to support a change to the commercial product specifications. If Applicant wishes to expand/change commercial product specifications post-licensure, this has to be done via well designed clinical studies after discussion with the FDA.
4. During the ongoing discussion of (b) (4) with the Agency, Janssen has worked to align with Agency's expectations of (b) (4) both as a (b) (4) release assay and as an CPP in the DP process. In the response to IR23, Janssen tightened the PAR of the (b) (4) parameter in the DP process from (b) (4) of the target (b) (4) based on limitations of the development study data to support this range over the full (b) (4) release specification at that time of (b) (4). Following the further discussion with the Agency regarding the (b) (4) assay, Janssen removed the (b) (4) assay from the (b) (4) release panel due to an incomplete validation package for the assay and committed to implementing a (b) (4) of (b) (4) for all (b) (4) batches used in the DP manufacturing process in the response to IR25. With the (b) (4), Janssen would like to propose maintaining the original PAR in the DP process as (b) (4) of the target (b) (4) for an (b) (4) of (b) (4). While previously tightened to (b) (4) due to limited data over the acceptable (b) (4) range, the development studies in 3.2.S.2.6 support (b) (4) of the target (b) (4) as the studies were performed at an (b) (4) of (b) (4). It would be appreciated if the Agency would consider reverting back to the (b) (4) PAR with the (b) (4) set at (b) (4).
- FDA confirmed that the information will be reviewed.



5. Regarding the comparability protocols (CPs) filed in the 3.2.R. section, when does the Agency anticipate being able communicate their assessment on the downgrade requests within those CPs? If modifications are required, Janssen would like to discuss these with the Agency while the BLA remains in review.
  - FDA confirmed that the information is currently under review and an assessment will be sent as soon as possible.
6. Janssen presented the current capacity plan at (b) (4) during the PAI (b) (4). The capacity plan currently supports up to (b) (4) batch starts per (b) (4) for clinical/commercial patients. Without any additional physical expansion, up to (b) (4) batch per (b) (4) can be supported with additional Aseptic Processing Study data and the other justifications provided from the capacity assessment (i.e., staffing, QC testing, warehousing, supply inventory etc.). In an effort to proactively prepare for future capacity, what is the recommendation from the Agency on the mechanism to submit the capacity increase and can this be achieved by submitting a comparability protocol as a post approval supplement to support ongoing capacity efforts within the current facility design?
  - FDA agreed that submitting a comparability protocol as a post approval supplement can be used to support a capacity increase.

#### 8. Wrap-up and Action Items

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.