



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 and Rachel Blasdell at 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/OOD/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 autoleucl. 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 autoleucl. 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) [REDACTED]. 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.