



Our STN: BL 125746/0

**MID-CYCLE COMMUNICATION
SUMMARY**
August 25, 2021

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

Dear Dr. Nair:

Attached is a copy of the summary of your July 29, 2021 Mid-Cycle Communication 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 as soon as possible.

Please include a reference to STN BL 125746/0 in your future submissions related to your ciltacabtagene autoleucel 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

Mid-Cycle Communication Teleconference Summary

Application type and number: BLA 125746/0
Product name: ciltacabtagene autoleucl
Proposed Indication: 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: Janssen Biotech, Inc.
Meeting date & time: July 29, 2021, 11:00-12:00 ET
Committee Chair: Zhaohui Ye, PhD
RPMS: Nadia Whitt and Rachel Blasdell

FDA Attendees:

Meghna Alimchandani, MD, CBER/OBE
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
Colleen Caldwell, MS, MPH, CBER/OTAT/DRPM
Dennis Cato, CBER/OCBQ/DIS/BMB
Maitreyi Chattopadhyay, PhD, CBER/OTAT/DCGT
Haecin Chun, MT(ASAP)SBB, MS, CBER/OCBQ/DIS/BMB
Tianjiao Dai, PhD, CBER/OBE/DB
Donald Ertel, CBER/OCBQ/DMPQ
Zakaria Ganiyu, MS, MBA, CBER/OTAT/DRPM
Karla Garcia, MS, CBER/OCBQ/DBSQC
Bindu George, MD, CBER/OTAT/DCEPT/CHB
Bindu Kanapuru, CDER/OND/OOD/DHMII
Megha Kaushal, MD, CBER/OTAT/DCEPT
Anna Kwilas, PhD, CBER/OTAT/DCGT
Carolyn Laurencot, PhD, CBER/OTAT/DCGT
Jun Lee, PharmD, PhD, CBER/OCBQ/DCM/APLB
Wei Liang, PhD, CBER/OTAT
Jing Lin, PhD, CBER/OCBQ/DBSQC
Tiffany Lucas, PhD, CBER/OTAT/DCGT
Uendra Mahat, MD, CBER/OTAT/DCEPT
Leyish Minie, MSN, RN, CBER/OTAT/DRPM
Brad Moriyama, PharmD, BCCCP, CDER/OSE/DRM
Kavita Natrajan, MD, CBER/OTAT/DCEPT
Manette Niu, MD, CBER/OBE/DE
Steven Oh, PhD, CBER/OTAT/DCGT
Joseph Paradis, CDER/OSE/DRM
Lori Peters, CBER/OCBQ/DMPQ
Graeme Price, PhD, CBER/OTAT/DCGT/GTIB

Raj Puri, MD, PhD, CBER/OTAT/DCGT
Kanaeko Ravenell, MS, SBB (ASCP), CBER/OCBQ/DIS/BMB
Carolyn Renshaw, CBER/OCBQ/DMPQ
Christopher Saeui, PhD, CBER/OTAT/DCEPT
Kimberly Schultz, PhD, CBER/OTAT/DCGT
Ramani Sista, PhD, CBER/OTAT/DRPM
Nancy Skeeter, MBA, CBER/OTAT/DRPM
Marc Theoret, MD, OCE
Edward Thompson, CBER/OTAT/DRPM
Neil Vora, PharmD, MBA, PMP, CDER/OSE/PMS
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

Agenda:

To provide a review update that includes any issues of concern that requires a discussion.

Discussion Summary:

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date.
 - a. Chemistry, Manufacturing, and Controls (CMC): The current method used for calculation of the lot release potency ((b) (4)) result is not sufficient in controlling biological activity of the product. Janssen has been notified of this issue in Information Request #11 on July 9, 2021.
 - b. Clinical: The occurrence of recurrent grade 3 or 4 cytopenias and movement disorder following cilta-cel administration are additional safety concerns identified during our review. We recommend that these safety concerns be communicated to health care providers via information in the package insert and other appropriate risk mitigation measures such as the REMS training materials if a marketing approval is granted.

A pooled approach with respect to the neurologic toxicities related to movement disorder associated with the product as opposed to categorizing them as different entities was emphasized especially as all of the different entities proposed by the Applicant relate to the Parkinson-like neurologic toxicity. In addition, given the limited number of subjects and limited follow up for these toxicities, the Agency stated that the full spectrum of the Parkinson-like neurologic toxicity, risk factors and success of mitigation measures cannot be definitively characterized to support “splitting” these

various entities that fall under the umbrella of a movement disorder suggestive of Parkinson-like toxicity. “Splitting” of these Parkinson’s-like toxicities minimizes the rate of these movement disorder related AEs, which impacts adequate conveyance to the prescriber regarding the severity and rate of such events.

The concern for both prolonged and recurrent cytopenias especially those persisting or occurring beyond 6 weeks following study product administration was raised. Consequences of prolonged and/or recurrent cytopenias were discussed, to include the need for autologous stem cell rescue, risk of infection, alloimmunization in transfused subjects continued growth factor support, need for long-term infectious disease prophylaxis and inability to receive subsequent anti-myeloma therapy upon disease progression. Akin to neurologic toxicity, the need for this information to be communicated in the label and REMS was reiterated.

- c. Clinical: Discuss assessment of stringent CR (sCR) for subjects with bone marrow evaluations prior to date of biochemical response.

FDA stated that 17 subjects had bone marrow evaluations prior to a biochemical response. Eight subjects had evaluations outside of the 30-day window timepoint. The Agency stated that the Applicant has not provided evidence to support that if these evaluations are done in advance, the BM assessments will remain negative. The Agency informed the Applicant that if no evidence can be provided, then the Agency may downgrade the responses or the best response date would change to a date when a subsequent marrow was performed.

The Agency stated for a single arm trial more clarity would be needed to understand the impact of bone marrow assessments that were performed well before a patient achieved a CR biochemically.

Janssen proposed to provide subsequent bone marrow data for the 8 subjects. FDA stated this would be acceptable and we would adjudicate the response in relation to the timing of these assessments.

2. Information regarding major safety concerns.

Please see above.

3. Preliminary Review Committee thinking regarding risk management.

- a. We have determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of CARVYKTI® outweigh the risks of Cytokine Release Syndrome and Neurologic Toxicity. We are reviewing the proposed REMS program for CARVYKTI® and will be in communication with you regarding details of the REMS program at a later date.

b. The pharmacovigilance plan for CARVYKTI® includes a long-term follow-up registry of CARVYKTI® recipients; the preliminary protocol is under review.

4. Any information requests sent, and responses not received.

- Clinical Pharmacology IR sent on June 23, 2021; requested Janssen response by July 28, 2021. – Has been received
- Manufacturing facility IR sent on July 9, 2021; requested Janssen response by July 30, 2021.
- Epidemiology IR sent on July 19, 2021; requested Janssen response by July 30, 2021.
- REMS document IR sent on July 26, 2021; requested Janssen response by August 2, 2021.
- CMC IR sent on July 27, 2021; requested Janssen response by August 4, 2021
- Clinical IR sent on July 28, 2021; requested Janssen response by August 11, 2021

5. Any new information requests to be communicated.

The review team has no new information requests to be communicated at this time.

6. Proposed date for the Late-Cycle meeting (LCM).

The LCM between you and the review committee is currently scheduled for September 20, 2021, and the LCM Materials will be sent on or before September 10, 2021.

If these timelines change, we will communicate updates to you during the course of the review.

7. Updates regarding plans for the AC meeting.

There are no plans to present this Biologics License Application (BLA) to the Cell Gene Therapy Advisory Committee (CGTAC) at this time.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.

Tentative Labeling Target Date: October 29, 2021

Tentative PMC Target Date: October 29, 2021

9. Additional Discussion:

The applicant requested information on whether there was a projected timeline for receipt of FDA revisions to the additional REMS materials. FDA stated that at this time there is no projected timeline, and it will depend on labeling negotiations and acceptance of labeling changes.

The applicant acknowledged that they were informed of the delayed inspection date for the (b) (4) facility. FDA informed the applicant that the Agency is committed, if resources permit, to performing the inspection in the September to mid-October timeframe. FDA informed the applicant that at this time there is no plan to delay the PDUFA due date but that the final determination will depend, in part, on the outcome of the inspection. Janssen informed FDA that they are willing to send any documents needed prior to the inspection to help facilitate the timeline. FDA acknowledged and thanked Janssen for this proposal and will inform them if this will be needed.