Our STN: BL 125376/0

MID-CYCLE COMMUNICATION SUMMARY
DECEMBER 10, 2020

Celgene Corporation
Attention: Pinky Doshi, MS
86 Morris Ave
Summit, NJ 07901

Dear Ms. Doshi:

Attached is a copy of the summary of your November 19, 2020 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 125376/0 in your future submissions related to idecaptagene vicleucel (ABECMA®).

If you have any questions, please contact Juliane Carvalho or Colleen Caldwell, at (301) 796-3927 or (240) 315-6270, respectively.

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

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Mid-Cycle Communication Teleconference Summary

Application type and number: BL 125736/0
Product name: idecaptagene vicleucel (ABECMA®)
Proposed Indication: For the treatment of adult patients with multiple myeloma who have received at least three previous therapies with an immunomodulatory agent, a proteasome inhibitor and/or an anti CD38 antibody.
Applicant: Celgene Corporation
Meeting date & time: Thursday, November 19, 2020 11:00 AM-12:30 PM
Committee Chair: Anna Kwilas, PhD
RPMs: Juliane Carvalho, MS and Colleen Caldwell, MS, MPH

FDA Attendees:
Meghna Alimchandani, MD, CBER/OBE
Rachael Anatol, PhD, CBER/OTAT
Kimberly Benton, PhD, CBER/OTAT
Wilson Bryan, MD, CBER/OTAT
Juliane Carvalho, MS, CBER/OTAT/DRPM
Colleen Caldwell, MS, MPH, CBER/OTAT/DRPM
Nannette Cagungun, MS, PD, RAC, CBER/OTAT/DRPM
Jessica Chery, PhD, CBER/OTAT/DCGT
Zakaria Ganiyu, MS, MBA, CBER/OTAT/DRPM
Denise Gavin, PhD, CBER/OTAT/DCGT
Ravi Goud, MD, CBER/OBE/DE/AEB
Shana Hardy, PhD, CBER/OTAT/DCEPT
Dana Jones, PhD, CBER/OCBQ/DCM/APLB
Beatrice Kallungal, MS, CBER/OTAT/DRPM
Bindu Kanapuru, CDER/OND/OOD/DHMII
Lily Koo, PhD, CBER/OCBQ/DMPQ
Anna Kwilas, PhD, CBER/OTAT/DCGT
Bo Liang, PhD, CBER/OTAT/DCGT
Wei Liang, PhD, CBER/OTAT/DCEPT
Xue (Mary) Lin, PhD, CBER/OBE
Jiang Liu, CDER/OTS/OCP/DPM
Anthony Lorenzo, CBER/OCBQ/DMPQ
Randa Melhem, PhD, CBER/OCBQ/DMPQ
Darya Melnyk, CBER/OCBQ/DBSQC
Steven Oh, PhD, CBER/OTAT/DCGT
Yen Phan, MLS(ASCP)CM, CBER/OCBQ
Raj Puri, MD, PhD, CBER/OTAT/DCGT
Jakob Reiser, PhD, CBER/OTAT/DCGT
Carolyn Renshaw, CBER/OCBQ/DMPQ
Lisa Stockbridge, PhD, CBER/OCBQ/DCM/APLB
Marc Theoret, MD, OCE
Deborah Thompson, MD, MSPH, CBER/OBE

Nicole Trudel, CBER/OCBQ/DMPQ
Xiaofei Wang, PhD, CBER/OTAT/DCEPT
Yaning Wang, CDER/OTS/OCP/DPM
Nadia Whitt, CBER/OTAT/DRPM
Yuan Xu, CDER/OTS/OCP/DPM
Iryna Zubkova, CBER/OCBQ/DMPQ/ARB

Applicant attendees:
Tim Belt, Global Regulatory (CMC), Bluebird bio
Joseph Dymkowski, Drug Safety
Jason Treese, CTDO Quality Assurance
Ramola Bhandarkar, Global Regulatory Sciences, Bluebird bio
Renea Faulknor, Global Regulatory, CMC
Anna Truppel-Hartmann, Global Drug Development, Bluebird bio
Tim Campbell, Global Drug Development
Kristen Hege, Global Drug Development
Ellen Schumacher, Commercial Regulatory Affairs
Wendy Corbett, Global Regulatory Sciences
Liping Huang, Biostatistics
Christopher Wiwi, CTDO (CMC)
Jamie Connarn, Clinical Pharmacology
Qian Li, Biostatistics
Mandy Xie, CTDO (CMC)
Hiufung Chu, Global Regulatory (CMC), Bluebird bio
Jane Lin, Global Regulatory Sciences
Agnes Yeboah, Global Regulatory, CMC
Pinky Doshi, Global Regulatory Sciences
Patel Payal, Global Drug Development
(b) (4), CTDO (BMS Oversight for (b) (4))
Jennifer Dudinak, Global Regulatory Sciences
Rosanna Ricafort, Global Drug Development

Agenda:

To discuss the progress of the BLA review

Discussion Summary:

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date.

    a. **CMC**:
    Discussions regarding the validation of anti-BCMA02 CAR lentiviral vector (LVV) and idecaptagene vicleucel (ide-cel) analytical assays, LVV and ide-cel process characterization and control as well as LVV and ide-cel specifications are ongoing.

Meeting discussion:
The CMC team just completed review of the LVV and ide-cel process characterization and controls submitted to support the BLA. The FDA submitted a CMC information request (IR #28) on November 19, 2020 with responses due date of Friday, December 4, 2020 to communicate the Agency's concerns regarding the CMC information submitted to the BLA. The CMC team is currently reviewing the proposed LVV and ide-cel specifications and the applicant should expect to receive an information request regarding the proposed specifications soon.

b. **Clinical**:
Issues regarding efficacy adjudication were discussed with the Applicant in a teleconference held on 11/9/2020. IR requesting updated efficacy datasets based on Agency's efficacy re-adjudication has been sent to the applicant.

Meeting discussion:
The FDA reiterated that the clinical team does not have any issues that need to be communicated to the applicant at the mid-cycle communication meeting. The clinical team has handled the review issues interactively via information requests and an informal teleconference held with the applicant on November 9, 2020.

c. **DMPQ (CMC facility and equipment):**
The following significant deficiencies are included in a CMC facility and equipment information request sent to the Applicant on November 17, 2020.

i. Cleaning validation for (b) (4) critical filling equipment with indirect product contact at the (b) (4) facility is not provided.

ii. The use of the (b) (4) autoclave ((b) (4) autoclaves) to sterilize (b) (4) critical filling equipment with indirect product contact at the (b) (4) facility is not validated.

iii. Insufficient information and data were provided for (b) (4) decontamination cycle validation to support (b) (4) decontamination of the (b) (4) at the (b) (4) facility.

iv. Requalification of the biological safety cabinets (BSCs) under (b) (4) conditions in response to the microbial excursions (including mold) during the initial 2018 environmental qualification (EMPQ) at the (b) (4) facility was not provided.

v. Sampling results for (b) (4) at point-of-use in rooms used for anti-BCMA CAR lentiviral vector manufacture were not provided.

vi. Lack of microbial environmental control in the Grade (b) (4) areas in the Celgene S12 facility. Specifically, viable excursions in Grade (b) (4) areas were reported at elevated rates during (b) (4) amic conditions. This is consistent with the numerous surface viable and personnel viable excursions reported in the Grade (b) (4) environment during aseptic process validation.

vii. Environmental monitoring data derived from the capacity ramp study at the Celgene facility were not provided.

viii. Ide-cel drug product shipper qualification and shipping validation studies did not test the maximum shipping load against mechanical distribution challenges.

ix. Disinfectant effectiveness studies performed at (b) (4) and Celgene S12 facilities did not include model viruses.

Meeting discussion:
The FDA submitted a DMPQ information request (IR #27) on November 17, 2020 with responses due date of December 8, 2020 to communicate the Agency's concerns, some of which are listed in mid-cycle communication teleconference agenda. The FDA reiterated the DMPQ IR has all the items listed in the mid-cycle communication agenda in more detail and the Agency expects the applicant's IR responses by the requested due date.

The applicant acknowledged the receipt of DMPQ IR from November 17, 2020 and the CMC IR from November 19, 2020. The FDA should expect the DMPQ IR responses by December 8, 2020. The applicant is currently reviewing the CMC IR # 28 sent on November 19, 2020 and will communicate if they have any questions or concerns.

2. Information regarding major safety concerns.

   a. There are no major safety concerns identified at this time.

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 ABECMA® outweigh the risks of Cytokine Release Syndrome and Neurologic Toxicity. We are reviewing the

proposed REMS program for ABECMA® and will be in communication with you regarding details of the REMS program at a later date.

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

4. Any information requests sent and responses not received.

   a. An information request was sent on November 17, 2020 regarding CMC facility and equipment. Complete responses are expected on December 8, 2020.

5. Any new information requests to be communicated.

   a. CMC: There are no requests to be communicated at this time. An information request regarding proposed LVV and ide-cel specifications is currently being prepared.

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

   a. The LCM with the applicant is currently scheduled for January 29, 2021.

   b. The LCM materials to be sent to the applicant by January 19, 2021.

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

7. Updates regarding plans for the AC meeting.

   a. There are no plans for advisory committee meeting at this time.

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

   a. There are no changes at this time.

9. Applicant Agenda Items to be discussed, if time permits:

   a. **APLB:** *To allow the Sponsor to plan for pre-clearance of promotional materials with APLB, in light of the potential limitations of Agency review timelines during the ongoing COVID19 pandemic, discuss if the Agency can provide insights on the approval pathway for ide-cel.*

      The review timelines for promotional materials remain the same. The applicant should contact the FDA if they have a plan for submission of launch

promotional material. Pre-clearance is not necessary unless this will be accelerated approval or REMS.

Meeting discussion:
The applicant inquired whether the FDA would have timeline for submission of the promotional materials and whether a decision had been made regarding possible accelerated approval. The FDA stated the review is ongoing and the Agency does not have a decision regarding accelerated approval at this time, but FDA will communicate this decision to the applicant as soon as a decision is made.

b. **DMPQ:** *Given the ongoing COVID19 pandemic, can FDA kindly share thoughts of potential timing of the pre-license inspections for the ide-cel BLA, and whether the timing could be impacted by COVID19?*

Inspections of the (b) (4) facility (FEI: (b) (4) ; (b) (4)) and the Celgene Corporation facility (FEI: 3004991673; Summit, NJ, USA) are required before the application can be approved. FDA must assess the ability of these facilities to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel we may be unable to conduct inspections of the (b) (4) facility and the Celgene Corporation facility prior to the User Fee Date. We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

Meeting discussion:
The applicant acknowledged the impact of COVID-19 pandemic on FDA inspection of facilities. Celgene communicated their capability to host virtual inspections or partial inspections if needed and agreed to by FDA. The FDA stated that the Agency currently does not have the authority to conduct virtual facility inspections. Therefore, the FDA cannot accept the applicant's offer to accommodate a virtual facility inspection at this time.

END