Our STN: BL 125376/0

LATE-CYCLE MEETING MEMORANDUM
February 26, 2021

Celgene Corporation, a Bristol-Myers Squibb Company
Attention: Pinky Doshi, MS
86 Morris Ave
Summit, NJ 07901

Dear Ms. Doshi:

Attached is a copy of the memorandum summarizing your January 29, 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 STN BL 125376/0 in 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
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Silver Spring, MD 20993
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Late-Cycle Meeting Summary

Meeting Date and Time:	Friday, January 29, 2021 10:00 AM-11:30 AM
Meeting Location:	Webex Teleconference
Application Number:	BL 125736/0
Product Name:	idecaptagene vicleucel (ABECMA®)
Proposed Indications:	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 Name:	Celgene Corporation, a Bristol-Myers Squibb Company
Meeting Chair:	Anna Kwilas, PhD
Meeting Recorder:	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
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Denise Gavin, PhD, CBER/OTAT/DCGT
Bindu George MD, CBER/OTAT/DCEPT
Ravi Goud, MD, CBER/OBE/DE/AEB
Shana Hardy, PhD, CBER/OTAT/DCEPT
Anthony Hawkins, MS, CBER/OCBQ/DIS/BMB
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
Xue (Mary) Lin, PhD, CBER/OBE
Jiang Liu, CDER/OTS/OCP/DPM
Anthony Lorenzo, CBER/OCBQ/DMPQ
Darya Melnyk, CBER/OCBQ/DBSQC
Marie Anderson, PhD, CBER/OCBQ/DBSQC
Steven Oh, PhD, CBER/OTAT/DCGT
Yen Phan, MLS(ASCP)^{CM}, CBER/OCBQ
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Yuan Xu, CDER/OTS/OCP/DPM
Iryna Zubkova, CBER/OCBQ/DMPQ/ARB

APPLICANT ATTENDEES
Mathias Hukkelhoven, SVP - Global Regulatory Strategy and Policy
Jennifer Dudinak, SVP - Global Regulatory Strategy and Policy
Wendy Corbett, VP - Global Regulatory Strategy and Policy
Narin Ahmed, Senior Director - Global Regulatory Strategy and Policy
Pinky Doshi, Director - Global Regulatory Strategy and Policy
Jane Lin, Senior Manager - Global Regulatory Strategy and Policy
Annie Sturgess, VP - Global Regulatory Science CMC
Agnes Yeboah, Executive Director - Global Regulatory Science CMC
Renea Faulknor, Manager - Global Regulatory Science CMC
Ann Lee, SVP - Global Product Development and Supply
Thomas Damratoski, Executive Director - Global Product Development and Supply
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Ryan Shorr, Associate Director - Global Product Development and Supply
Jaymes Fuller, Senior Manager - Global Product Development and Supply
Christopher Wiwi, Senior Director, Global Product Development and Supply
Jason Treese, - Executive Director, CTDO Quality Assurance
Krishnan Viswanadhan, SVP - Global Cell Therapy Franchise Lead
Olivier Gouedard, SVP - Global Cell Therapy Franchise, ide-cel Program Lead
Rosanna Ricafort, VP - Cell Therapy Clinical Development
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Tim Campbell, Senior Director - Early Clinical Development Lead
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Liping Huang, Associate Director - Biostatistics
Jamie Connarn, Senior Research Investigator - Clinical Pharmacology
Roelf Zondag, Director - Global Medical Affairs Operation
Gil Granados, Director - Global Regulatory Labeling
George Marchesini, Director - US Commercial Regulatory Affairs
Anna Truppel-Hartmann, Vice President - Global Drug Development (bluebird bio)
Ramola Bhandarkar, Senior Director - Global Regulatory Science (bluebird bio)

Hiufung Chu, Associate Director - Global Regulatory Science CMC (bluebird bio)
Tim Belt, Senior Director - Global Regulatory Science CMC (bluebird bio)

BACKGROUND

BLA 125736/0 was submitted on July 27, 2020 for 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.

PDUFA goal date: March 26, 2021

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on January 19, 2021.

MEETING DISCUSSION

Clinical Dose Range

FDA comment: Preliminary efficacy assessment supports a dose range of 300-460 $x10^6$ CAR+ T cells.

The Applicant agreed with the Agency's proposal to limit the lower dose range to 300 $x10^6$ CAR+ T cells, but stated that capping the upper end of the dose range at 460 X 10^6 CAR+ T cells will hamper the ability to deliver a dose close to 450 X 10^6 CAR+ T cells given the commercial fill strategy. Given the dose response relationship observed in Study MM-001 (numerically higher ORR, CR and median DOR in 450 $x10^6$ versus 300$x10^6$ CAR+T cell dose cohort) and the manageable toxicities of 450 $x10^6$ dose cohort, the Applicant proposed to target a dose closer to 450 $x10^6$ within the recommended dose range by proposing to extend the upper limit for the dose range to (b) (4) . Extending the upper end of the dose range to (b) (4) CAR+ T cells will allow use of the validated commercial fill process to deliver a dose close to 450 $x10^6$ CAR T cells.

The applicant inquired if there was any flexibility to extend the higher end of the dose range above 460$x10^6$ CAR+T cells. The Agency noted that in determining the dose range, the response rate was assessed at increments within a dose cohort and the lower bound of the 95% CI was evaluated against the null hypothesis proposed in Study MM-001. Therefore, in determining extension of the upper end of the dose range, efficacy data at that higher dose range will have to be reviewed.

The Applicant stated that the safety data from 25 subjects treated with a dose of >460 $x10^6$ CAR+ T cells across studies MM-001, CRB-401, MM-001 Japan and MM-002, Cohort 1 is consistent with the safety profile observed at the target dose of 450 $x10^6$ CAR+ T cells. The Applicant asked if the Agency would be open to reviewing the efficacy

data from these 25 subjects to support the higher dose range. The Agency noted that MM-001 is the primary study supporting efficacy and the efficacy data from the remaining studies will require Agency's review and adjudication to determine if the risk benefit profile is favorable at the higher dose range. Therefore, the review of this additional efficacy data may add time to the review clock and could constitute a Major Amendment.

FDA noted that internal discussions are needed, and the Agency may be open to having further discussion with the Applicant.

CMC Drug Product Fill Strategy

FDA Comment: The Applicant was asked about the flexibility of the planned ide-cel drug product fill strategy, its ability to accommodate the FDA proposed tighter dose range, whether modifications to the fill strategy may be necessary to achieve this tighter dose range and, if modifications are necessary, whether additional process validation studies would also be necessary.

The Applicant confirmed that there will be no modifications to the ide-cel filling strategy to obtain the FDA proposed dose range, and therefore, no additional validation studies are needed. The Applicant also confirmed that this would result in administering a lower target dose to the patient.

CMC Manufacturing Capacity

FDA Comment: Based on the data provided in the (b) (4) capacity ramp study included in the initial BLA submission and the most recent (b) (4) capacity ramp test submitted in response to IR#38 Question 26, FDA is concerned regarding the Applicant's ability to successfully achieve the currently proposed capacity at the S12 facility of (b) (4) and the ability of the facility to accommodate future commercial production needs.

FDA restated that the capacity ramp test has a target release time of (b) (4) and, for (b) (4) lots in the (b) (4) capacity ramp test, that target date was not reached. Therefore, this part of the capacity assessment was not met, resulting in the completion of only (b) (4) . FDA noted that detailed information on the open deviations that led to the delay in product release and changes made to address the issues identified in the capacity ramp test were not provided.

FDA went on to state that while the Applicant provided general information on the corrective actions implemented to address the issues identified in the capacity ramp test, the Agency does not have data to support that the corrective actions resulted in the Applicant's ability to meet the proposed manufacturing capacity. FDA stated that since there is not detailed information to support if these actions were effective, the Agency cannot agree to the proposed (b) (4) . FDA further stated they cannot agree to the (b) (4) capacity at this time either based on the data provided by the Applicant.

FDA proposed that the best way forward is to further evaluate the S12 manufacturing capacity during the planned on-site inspection. FDA further stated that they would provide the Applicant a list of what the Agency would like to see during the inspection prior to inspection initiation.

The Applicant agreed with the Agency's proposal.

Facility Inspections

FDA noted that currently two inspection teams are working in parallel. The (b) (4) facility pre-license inspection is beginning on (b) (4) . FDA further stated that the inspection team has reached out to the Applicant regarding the Celgene S12 facility pre-license inspection, and the current date to begin that inspection is likely February 15, 2021. FDA stated that there will be more communication with the Applicant regarding inspection preparation.

The Applicant confirmed that they are in communication with the Agency and have confirmed their readiness for inspection on February 15, 2021.

The Applicant asked the Agency if they plan on inspecting the (b) (4) facility based on a recent information request, they received regarding the testing facility.
FDA confirmed they are communicating with ORA, and there is the possibility that they will inspect the (b) (4) facility as well. FDA further stated they would let the Applicant know as soon as possible if the (b) (4) facility inspection will take place, and they would inform (b) (4) as well.

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. There was no further discussion during the meeting.

INFORMATION REQUESTS DISCUSSED DURING THE MEETING

FDA stated that the responses to Information Requests #42 and #43 were already received. The Agency has sent an additional three Information Requests to the Applicant:

- IR #44 (Clinical): the Applicant response was received by the Agency
- IR #45 (CMC): the Applicant confirmed their response is on track to be sent to the Agency on Monday , February 1, 2021

- IR #46 (Labeling): partial PI was sent to the Applicant with clinical comments only; the Applicant response is expected Thursday, February 4, 2021

The Applicant asked when the Agency anticipated sending comments on the rest of the label.

FDA stated that they currently do not have a timeline they can share with the Applicant.

POSTMARKETING REQUIREMENTS/POSTMARKETING COMMITMENTS

In the LCM materials, FDA noted 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 idecabtagene vicleucel. 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, 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 idecabtagene vicleucel and the risk of all secondary malignancies occurring after treatment with idecabtagene vicleucel. The study will include at least 1500 adult patients with multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody; the enrolled patients will be followed for 15 years after product administration. FDA acknowledged the timetable proposed in the draft protocol for the post-marketing registry study, which includes the following milestones:

- Final protocol submission: May 31, 2021
- Study completion: June 30, 2041
- Final study report: June 30, 2042

In response to the Applicant's question included in the LCM pre-read slides, the Agency confirmed that 360 of the 1500 total patients may be enrolled from ide-cel ongoing and planned interventional clinical trials. FDA further stated that the 360 subjects must receive the approved dose, and this should be specified in the final study protocol.

The Applicant asked FDA to confirm that there were no further comments to the revised study protocol which was submitted with the response to IR #16.

FDA stated that there were no comments at this time.

ADDITIONAL APPLICANT QUESTIONS DURING THE MEETING

The Applicant provided eight questions in their LCM pre-read slides, and six were discussed during the meeting:

1. **Could the Agency please confirm that there will be no efficacy post-marketing requirement for ide- cel?**

Please see response to Question 2.

2. **Could the Agency please provide their current thinking on the approval pathway for ide-cel (traditional or Subpart E accelerated approval)?**

   FDA stated that internal discussions were ongoing and the Applicant will be informed when a final determination is made regarding the approval pathway for ide-cel and if an efficacy post-marketing study will be required.

3. **Could the Agency please comment on the timing to receive feedback on the BB2121-EAP-001 study?**

   The Applicant stated they would like to submit responses to any FDA comments to the IND as soon as possible so the study could begin right after BLA approval.

   FDA stated they anticipate comments will be provided to the Applicant within one to two weeks of any regulatory action taken on the BLA. FDA further requested that the Applicant submit the proposed release specifications for the EA protocol in an Amendment to the IND.

   The Applicant stated that the EAP product specifications would be the same as the current clinical product specifications and asked whether these specifications still need to be resubmitted, since the specifications are already in the IND. FDA stated that, if there are no changes, the specifications do not need to be resubmitted and the Agency will evaluate the current specifications when the protocol is evaluated, and no additional information is needed at this time.

4. **We acknowledge that the pre-license inspection PLI for** (b) (4) **sites has been scheduled to start on** (b) (4) **. Could the Agency please provide us an update on the scheduling of (PLI) for the Celgene S12 facility?**

   As per Applicant, there was no further discussion of this question during the remainder of the meeting as it was already discussed earlier in the meeting.

5. **Could the Agency please confirm if the Agency will be providing comments on 1st draft of the PI by Feb 25, as per the per Filing letter?**

   As per Applicant, there was no discussion of this question during the meeting.

6. **We acknowledge that the review is on-going. Based on the progress of the review to date, can the Agency share general thoughts on the status of the review and/or the potential for further substantive issues?**

   FDA stated that as issues have been identified during the review, the Agency has communicated them to the Applicant, and currently there are no additional substantive issues to convey at this time.

7. **Would the Agency provide guidance on how the efficacy data will be presented in Section 14 of the ide-cel PI?**

See comments below under Question 8.

8. **Would the Agency provide guidance on how the Efficacy Evaluable Patients will be defined for Section 14 of the ide-cel PI?**

   In response to Questions 7 and 8, FDA stated that it is premature to comment on Section 14 of the ide-cel PI. Section 14 is currently being reviewed by the Agency.

   FDA further stated that information regarding the leukapheresis population for the recommended dose range will be included in the label. FDA noted that after internal discussions, the Agency will communicate with the Applicant.

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.

Post Meeting comments:

Please note that any additional efficacy data that may be submitted for Agency's review should be adjudicated by the IRC (Independent Response Committee) based on IMWG 2016 guidelines. To allow for pooling of efficacy data across studies, the inclusion and exclusion criteria, definition of measurable disease, and schedule of disease assessments should be similar between these studies.

END