



Our STN: BLA 125789

**MID-CYCLE COMMUNICATION
SUMMARY**
April 8, 2024

Adaptimmune LLC
Attention: Eric Dollins, PhD
351 Rouse Boulevard
Philadelphia, PA 19112

Dear Dr. Dollins:

Attached is a copy of the summary of your April 3, 2024, 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 BLA 125789/0 in your future submissions related to the subject product.

If you have any questions, please contact Tigist Assefa by email at Tigist.Assefa@fda.hhs.gov.

Sincerely,

Beatrice Kallungal, MS
Director
Division of Review Management and Regulatory Review 1
Office of Review Management and Regulatory Review
Office of Therapeutic Products
Center for Biologics Evaluation and Research

Mid-Cycle Communication Teleconference Summary

Application Type and Number: BLA 125789
Product Name: afamitresgene autoleucel
Proposed Indication for Use: Treatment of adult patients with unresectable or metastatic synovial sarcoma who have received prior systemic therapy.
Applicant: Adaptimmune LLC
Meeting Date & Time: April 3, 2024, 11:00 AM – 12:00 PM EDT
Committee Chair: Elvira Argus, PhD
RPM: Tigist Assefa, PharmD

FDA Attendees:

Meghna Alimchandani, MD, CBER/OBPV/DPV
Rachael Anatol, PhD, CBER/OTP
Elvira Argus, PhD, CBER/OTP/OGT
Alan Baer, PhD, CBER/OTP/OGT
Katherine Barnett, MD, CBER/OTP/OCE
Peter Bross, MD, CBER/OTP/OCE
Asha Das, MD, CBER/OTP/OCE
Brendan Day, MD, CBER/OBPV/DPV/PB2
Maureen DeMar, CBER/OCBQ/DMPQ
Laura DeMaster, PhD, CBER/OTP/OGT
Denise Gavin, PhD, CBER/OTP/OGT
Christine Harman, PhD, OCBQ/DMPQ
Guo-Chiuan Hung, PhD, CBER/OTP/OGT
Abigail Johnson, RN, BSN, CBER/OTP/OCE
Paul Kluetz, MD, OCE/CDER
Anna Kwilas, PhD, CBER/OTP/OGT
Jessica Lee, MD, PhD, CBER/OTP/OCE
Doros Leslie, MD, CDER/OND/OOD/DOIII
Tyree Newman, MDiv, CBER/OTP/ORMRR
Y Nguyen, PhD, CBER/OTP/OGT
Andrey Sarafanov, PhD CBER/OTP/OPPT/DH/HB2
Viviana Ramirez, CBER/OCBQ/DMPQ/MRB2
Kimberly Schultz, PhD, CBER/OTP/OGT
Nicole Verdun, MD, CBER/OTP
Nadia Whitt, MS, CBER/OTP/ORMRR

Adaptimmune LLC Attendees:

Dennis Williams, SVP Late Stage Development
Eric Dollins, Head of Global Regulatory Affairs
Sara Brilha, Associate Director Global Regulatory Affairs
Anne-Marie McNicol, Senior Director Global Regulatory Affairs
Lon Pang, Associate Director Global Regulatory Affairs
Natalie Ward, Senior Director & Head of CMC Regulatory

Lane Jaeckle-Santos, Associate Director CMC Regulatory
Amita Gavaskar, Manager CMC Regulatory
Erin Van Winkle, Senior Director Clinical Development
Karen Chagin, SVP Early Stage Development
Michael Nathenson, Senior Medical Director Clinical Development
Jean-Marc Navenot, Senior Director Biomarkers
Elliot Norry, Chief Medical Officer
Lilliam Fernandes, Director Clinical Safety & Pharmacovigilance
Irving Ford, VP of Quality CMC
Mark Stielow, VP, Manufacturing & Technical Operations, MS&T, Product Development
Vinai Unnikrishnan, Director MS&T
(b) (6), MS&T Late Stage Lead
Joseph Sanderson, Senior Director Preclinical Research
Jane Bai, Principal Biostatistician

Discussion Summary:

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

Chemistry, Manufacturing, and Controls

- a. We do not agree that there is sufficient control of the (b) (4) manufacturing process (e.g., no in-process controls have been established for (b) (4)). In addition, we found the characterization of the (b) (4) steps to be inadequate. Specifically, it appears that you have not conducted process characterization (PC) studies to support the (b) (4) process (e.g., (b) (4)) during the (b) (4) manufacturing process.

Meeting Discussion for CMC Agenda item 1a:

Adaptimmune will address FDA's concern in their response to CMC information request (IR) #3 and inquired whether the FDA would be requesting specific in-process controls for the (b) (4) process. FDA responded that control of (b) (4) steps may be established through various approaches and stated an expectation that in-process controls for (b) (4) (e.g. (b) (4)) have acceptance criteria or action limits.

- b. We do not agree that the extractables and leachables assessment for the afami-cel drug product (DP) is adequate. You did not evaluate some of the high-risk process components in the extractables and leachables study(ies), which may result in underestimation of the leachables profile in the final product.

Meeting Discussion for CMC Agenda item 1b:

FDA informed Adaptimmune that in addition to the previous request to conduct an additional leachables study from process Step (b) (4) Step (IR sent on 03/26/2024) and reconstruct a full DP leachables profile based on both studies, it was found Adaptimmune had not submitted data from an actual extractables study for the major high-risk leachables components contacting (b) (4) process Step (b) (4). Thus, upon obtaining these data, they should be aligned with the extractables data "retrospectively" to ensure detection of any of non-targeted leachable, as regulations require conducting an extractable study first, followed by designing a leachables study to ensure targeting of all potential compounds. Adaptimmune commented that they will address the FDA's concerns including that in CMC IR#3.

Clinical

- a. The proposed indication is under review. We note that based on the most recent amendment of the protocol, Study ADP-0044-002 allowed enrollment of patients with metastatic or advanced unresectable disease who had previously received ifosfamide +/- doxorubicin in the pre-operative (neoadjuvant) or post-operative (adjuvant) primary tumor setting. These eligibility criteria may have led to a potentially heterogeneous population. The indication is generally based on the population represented in the study in which safety and effectiveness have been demonstrated.

Meeting Discussion for Clinical Agenda item 1a:

Adaptimmune requested for further clarification regarding what the heterogeneous population is referring to and its relation to the proposed indication.

FDA stated that the review is still ongoing for the proposed indication. In addition, the clinical review team noted that the eligibility criteria for Study ADP-0044-002 were revised in 2021 to allow enrollment of patients in the 1st line metastatic treatment setting if ifosfamide +/- doxorubicin was administered in either the pre-op (neoadjuvant) or post-op (adjuvant) setting. This may have led to enrollment of a heterogeneous population, which can impact interpretability of results.

- b. The review of the response assessment for Study ADP-0044-002 Cohort 1, is ongoing. As conveyed in clinical information request dated March 22, 2024, the response assessment in some subjects included in the efficacy analysis population, is confounded by on-study tumor biopsies of target lesions. FDA's evaluation regarding whether these patients should be excluded from the assessment of efficacy is ongoing.

Meeting Discussion for Clinical Agenda item 1b:

Adaptimmune requested FDA to elaborate on the physiological and mechanistic process in which the tumor biopsies impact tumor assessment.

FDA's analysis of response assessment is still ongoing. The clinical review team shared concern that on-study tumor biopsies of target lesions may confound response assessment for some patients. Therefore, some responders may be excluded from FDA's efficacy analysis, but this is still under review.

FDA pointed out that the IR response and CT images are still under review. In addition, FDA noted a discrepancy between the CT images annotated by independent review and the target lesion measurements in the ADLS dataset.

Adaptimmune is currently gathering CT images to provide to the FDA.

- c. Study ADP-0044-002 Cohort 2: Confirmatory Study. We refer to your BLA submission requesting accelerated approval (AA). For AA approval, FDA may request that the trial intended to verify clinical benefit be underway prior to approval. We note that you have previously proposed to submit data from Study ADP-0044-002 Cohort 2, as confirmatory evidence of afamitresgene autoleucel's benefit. Based on our review of the data from Cohort 1 of the study, the data from Cohort 2 do not appear adequate to verify clinical benefit should AA be granted. Specifically, we have identified the same major limitations of the response assessment as described in Clinical Comment #2. An additional potential limitation is that Study ADP-0044-002 Cohort 2 may be enrolling such a heterogeneous population as to potentially impact interpretability of study results. We recommend that you propose a new adequate and well controlled study that will facilitate a benefit: risk assessment in a clearly defined population.

Meeting Discussion for Clinical Agenda item 1c:

Adaptimmune previously proposed to use Cohort 2 from ADP-004-002 as the confirmatory study to verify clinical benefit. However, FDA noted the same limitations for Cohort 2 as just discussed above for Cohort 1. For the confirmatory study, FDA recommended Adaptimmune propose a new adequate and well-designed study that will allow benefit-risk assessment in a clearly defined population.

- d. Our review is ongoing and a Risk Evaluation and Mitigation Strategy (REMS) is under consideration at this time. Further information will be provided to the Applicant as our review progresses.

Meeting Discussion for Clinical Agenda item 1d:

Adaptimmune requested for additional information regarding requirement for REMS.

FDA responded that the review is ongoing, and a decision has not been made.

- e. We plan to send information requests on specific subjects as part of the ongoing assessment of the safety narratives. Specifically, we will be requesting information that will enable a comprehensive assessment of patients for whom these narratives were submitted.

Meeting Discussion for Clinical Agenda item 1e:

There was no discussion of this agenda item during the meeting.

- 2. Preliminary Review Committee thinking regarding a.) risk management, b) the potential need for any post-marketing requirement(s) (PMRs), and/or safety-related

PMCs, and c.) the ability of adverse event reporting and CBER's Sentinel Program to provide sufficient information about product risk.

Our review is ongoing. We will inform you when a decision has been reached concerning safety related PMR/PMC and REMS.

Meeting Discussion for Agenda item 2:

There was no discussion of this agenda item during the meeting.

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

CMC IR#3 was sent on March 26, 2024 with a response due date of April 5, 2024.

Meeting Discussion for Agenda item 3:

FDA informed Adaptimmune that responses for Clinical IR#11 and Clinical IR#12 are due April 5, 2024 and April 8, 2024 respectively.

4. Any new information requests to be communicated.

As the review continues, new information requests will be conveyed as needed.

Meeting Discussion for Agenda item 4:

There was no discussion of this agenda item during the meeting.

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

The LCM between you and the Review Committee is currently scheduled for May 20, 2024. We intend to send the LCM meeting materials to you approximately 10 days in advance of the LCM. If these timelines change, we will communicate updates to you during the course of the review.

Meeting Discussion for Agenda item 5:

There was no discussion of this agenda item during the meeting.

6. Updates regarding plans for the AC meeting.

Currently, an AC is not anticipated.

Meeting Discussion for Agenda item 6:

There was no discussion of this agenda item during the meeting.

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

Internal Late-Cycle

May 2, 2024, 11:05 AM - 11:55 AM EDT

Applicant Late Cycle (In-Person)

May 20, 2024, 12:00 PM - 1:00 PM EDT (Late-Cycle Meeting material will be sent by May 10, 2024)

Meeting Discussion for Agenda item 7:

There was no discussion of this agenda item during the meeting.

8. Discuss status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval. **Note:** Ensure notification of intent to inspect manufacturing facilities has been issued.
 - a. Adaptimmune's Navy Yard facility (Philadelphia, PA) will be inspected April 1-5, 2024.
 - b. (b) (4) facility (b) (4) will be inspected (b) (4) .
 - c. BIMO inspections are currently pending.

Meeting Discussion for Agenda item 8:

Adaptimmune requested for additional information regarding domestic BIMO inspections. FDA responded that BIMO cannot provide any comments regarding inspections.