



Our STN: BL 125789

**LATE-CYCLE
MEETING MEMORANDUM**

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

Dear Dr. Dollins:

Attached is a copy of the memorandum summarizing your May 20, 2024 Late-Cycle Meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting 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 Tigist Assefa at 301-957-6612 or 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

Late-Cycle Meeting Summary

Meeting Date and Time: May 20, 2024, 12:00 PM – 1:00 PM

Meeting Location: WO, Bldg 71, 1208/1210

Application Number: BLA 125789

Product Name: afamitresgene autoleucel

Proposed Indications: Treatment of adult patients with unresectable or metastatic synovial sarcoma who have received prior systemic therapy.

Applicant Name: Adaptimmune LLC

Meeting Chair: Elvira Argus, PhD

Meeting Recorder: Tigist Assefa, PharmD

FDA ATTENDEES

Meghna Alimchandani, MD, CBER/OBPV/DPV
Marie Anderson, PhD, CBER/OCBQ/DBSQC
Elvira Argus, PhD, CBER/OTP/OGT
Tigist Assefa, PharmD, CBER/OTP/ORMRR
Alan Baer, PhD, CBER/OTP/OGT
Katherine Barnett, MD, CBER/OTP/OCE
Eden Chane, MS, CBER/OTP/ORMRR
Asha Das, MD, CBER/OTP/OCE
Maureen DeMar, CBER/OCBQ/DMPQ
Laura DeMaster, PhD, CBER/OTP/OGT
Rachel Duddy, MS, CBER/OTP/ORMRR
Lola Fashoyin-Aje, MD, MPH, CBER/OTP/OCE
Alyssa Galaro, PhD, CBER/OTP/OPT
Alifiya Ghadiali, CBER/OCBQ/DMPQ
Christine Harman, PhD, OCBQ/DMPQ
Gaya Hettiarachchi, PhD, CBER/OTP/OPT
Abigail Johnson, RN, BSN, CBER/OTP/OCE
Anna Kwilas, PhD, CBER/OTP/OGT
Jessica Lee, MD, PhD, CBER/OTP/OCE
Anthony Lorenzo, CBER/OCBQ/DMPQ
Yves (Maurice) Morillon, PhD, CBER/OTP/OPT
Tyree Newman, MDiv, CBER/OTP/ORMRR
Y Nguyen, PhD, CBER/OTP/OGT

Lori Peters, CBER/OCBQ/DMPQ
Carolyn Renshaw, CBER/OCBQ/DMPQ
Andrey Sarafanov, PhD CBER/OTP/OPPT/DH/HB2
Kimberly Schultz, PhD, CBER/OTP/OGT
Ramani Sista, PhD, CBER/OTP/ORMRR
Xiaofei Wang, PhD, CBER/OTP/OCE

APPLICANT ATTENDEES

Dennis Williams SVP, Late-Stage Development
Eric Dollins, VP & Head of Global Regulatory Affairs
Sara Brilha, Associate Director Global Regulatory Affairs
Anne-Marie McNicol, Senior Director Global Regulatory Affairs
Natalie Ward, Senior Director & Head of CMC Regulatory
Lane Jaeckle-Santos, Associate Director CMC Regulatory
Erin Van Winkle, Senior Director Clinical 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
Sandra D'Angelo, Spearhead-1 Clinical Investigator
Brian Van Tine, Spearhead-1 Clinical Investigator

BACKGROUND

BLA 125789/0 was submitted on December 5, 2023 for afamitresgene autoleucel.
Proposed indication: Treatment of adult patients with unresectable or metastatic synovial sarcoma who have received prior systemic therapy.

PDUFA goal date: August 4, 2024

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on May 10, 2024.

DISCUSSION

1. Discussion of Substantive Review Issues

The following substantive review issues have been identified to date:

Clinical

- Study conduct irregularities affecting data quality and interpretability necessitating a new independent third-party re-review of response assessment for the 44 subjects in Cohort 1 of Study ADP-0044-002 using a different vendor.

Meeting Discussion

Adaptimmune requested clarification on the specifics of the data quality issues and how the data from the re-review will be utilized by the FDA. FDA re-iterated concerns over issues related to study conduct and data integrity, including evaluation and assessment of response, as detailed in the late cycle agenda and numerous information requests. FDA maintains that they have concerns about the reliability of the primary efficacy assessment, especially in the context of the small study size. To address these concerns, FDA requests a re-review of response assessment with a different vendor. In order to minimize bias and ensure a blinded independent review, FDA requests a re-review of all 44 patients in Cohort 1. FDA stated that the data from the re-review is necessary to support the regulatory decision on the application. Adaptimmune agreed to conduct a re-review of all 44 subjects in Cohort 1 with a new vendor.

Adaptimmune also requested clarification on the format of the re-reviewed data for submission to the BLA. FDA requested a copy of the Independent Review Charter (IRC) that will be used for the independent re-review. This should be submitted as an amendment to the BLA for FDA to review prior to beginning the re-review. FDA stated that they will be available to provide feedback in a timely fashion without delay. Adaptimmune can request a meeting, or a written response and FDA will provide timely feedback on the IRC.

In addition to the IRC, the FDA requested:

- CVs of the new independent reviewers and adjudicator
 - A revised version of the efficacy datasets with the new independent reviewer assessments
 - A brief report that includes a summary table with re-calculated objective response rate and duration of response data
 - Annotated independent reviewer images for those subjects assessed as responders by re-review
 - Subject level listing of all subjects identified as responders by re-review with the response assessment of each independent reviewer at each imaging time point. Provide in tabular format
 - A list of subjects who required adjudication following the IRC
- As discussed during the mid-cycle meeting, your plan to verify clinical benefit based on data from Study ADP-0044-002 Cohort 2 (i.e., should approval be granted), will not be adequate. Discuss your plan to verify clinical benefit based on an adequate and well controlled study.

Meeting Discussion

Adaptimmune requested clarification on FDA's concern over the previously discussed plan to use cohort 2 as confirmatory clinical evidence. FDA stated that, after identifying the data quality issues and the observed study conduct issues in Cohort 1, the Agency is concerned that these same issues may very likely be present in Cohort 2. Therefore, FDA is concerned about the

acceptability of using data from Cohort 2 to verify clinical benefit should accelerate approval be granted.

Adaptimmune asked if a re-review of response assessment for subjects in Cohort 2 with the new vendor would address this concern. FDA pointed out that there were several review issues with Cohort 1 as detailed in the mid-cycle agenda, numerous information requests (IR), and the late cycle agenda. Upon detailed review of these data, FDA is concerned that the same review issues may be present in Cohort 2. Adaptimmune stated that they are currently enrolling patients in a Cohort 3 on ADP-0044-002. FDA recommended that Adaptimmune revise Study ADP-0044-002 protocol to address FDA's concerns. In addition, Adaptimmune should submit a new proposal for confirmatory evidence to verify clinical benefit and request a meeting or written response for FDA feedback. FDA discussed the importance of prompt completion of the confirmatory trial to ensure timely verification of clinical benefit.

•(b) (4)

[REDACTED]

[REDACTED]

CMC

- Analytical assessment of leachables in the DP is incomplete due to the lack of both extractables and leachables profiles for (b) (4) major process components utilized in Step (b) (4) of the afamitresgene autoleucel manufacturing process. In response to a CMC IR received on April 30, 2024 (Question 1), you stated that the extractables data from these components are not available, while the risk of leachables from them is “considered low”, without performing an assessment requested by FDA on March 26, 2024 (Question 4c). If the requested data cannot be provided within the BLA review timeline, a PMR may be required.

Meeting Discussion:

Adaptimmune proposed an additional study post-approval of the (b) (4) consumables used during (b) (4)

[REDACTED] and asked if their proposal is sufficient to mitigate concern. FDA stated that the proposed study design is generally acceptable. However, the study design does

not account for the cumulative nature of leachables in the DP from Steps (b) (4) and (b) (4) steps. FDA clarified that for a correct assessment, the AET should be decreased by (b) (4) in each of the (b) (4) proposed consumables studies and in the completed container closure system (CCS) study. FDA stated that an alternative, more straightforward, study design may be acceptable, in which the manufacturing process for Steps (b) (4) is simulated and leachables are analyzed from a single sample. In this case, the respective AETs for this study and the completed CCS study should be lowered by (b) (4), and leachable profiles from the two studies should be added to reconstruct the overall profile in the DP. Adaptimmune agreed that the alternative study design may be favorable and indicated that a new study protocol would be developed and submitted to FDA for review prior to study initiation. In addition, Adaptimmune agreed to provide a new risk assessment once the new study is completed.

- There is an outstanding issue with lack of sufficient in-process controls in the (b) (4) manufacturing process. Specifically, you provided data indicating that the (b) (4) during (b) (4) operations are adequate but has not implemented in-process controls with acceptance criteria.

Meeting Discussion:

Adaptimmune proposed (b) (4) in-process controls (IPCs): (b) (4)

(b) (4) FDA responded that the lack of IPCs with acceptance criteria for (b) (4) remains an outstanding concern and that IPCs for (b) (4) at the (b) (4)

manufacturing process FDA clarified that they are not requesting that additional testing be performed but are requesting that acceptance criteria be established for the testing already in place in the (b) (4) manufacturing process.

- The sampling time point for DP identity testing is not appropriate. (b) (4) and identity testing is conducted on a (b) (4) sample, (b) (4). You currently do not confirm product identity using a final formulated DP sample.

Meeting Discussion:

Adaptimmune agreed to perform (b) (4) testing on the final formulated drug product (DP). The DP sample will be taken at (b) (4) as proposed in the response to CMC IR #4 dated May 8, 2024. FDA confirmed they are reviewing Adaptimmune's response to the CMC IR, specifically the proposed time point of QC sampling and will follow up with IRs as needed.

DMPQ

- Shipping validation for the afamitresgene autoleucel drug product is deficient in demonstrating the DP primary container remains integral after shipping simulation as was evidenced by observance of broken ports/tubing after shipping resulting in leaking bags. We are currently reviewing the response received May 8, 2024 to the IR sent April 26, 2024 to evaluate if acceptable. Potentially, a PMC may be required.

Meeting Discussion:

Adaptimmune acknowledged that damage was observed for (b) (4) subjected to simulated shipping within the transport simulation study performed and reported in VAL 02495.

Adaptimmune proposed to provide data mid-June 2024 from a simulated shipping study assessing:

1. The hypothesis for the previous damage observed.
2. Conditions expected for shipments of drug product within the U.S. using pallets for transport.

Additionally, Adaptimmune proposed the shipping design for the study which included sterility and container closure integrity testing after shipping simulations.

FDA will review the data when submitted in Mid-June.

- CCIT method sensitivity used for the DP (b) (4) was not defined. Additionally, the CCIT study provided to support the (b) (4) was performed on (b) (4) that were (b) (4), thus are not representative of the manufacturing process. We are reviewing the response received May 8, 2024 to the IR sent April 26, 2024 to evaluate if the response is acceptable. Potentially, a PMC may be required.

Meeting Discussion:

Adaptimmune proposed to provide data mid-June 2024 for validation of the (b) (4) test for (b) (4) DP (b) (4) container closures. Adaptimmune confirmed that the (b) (4) for the study will be filled at (b) (4)

- The 483 response, received April 26, 2024, to the inspectional observations from the Pre-License Inspection conducted for the Adaptimmune Navy Yard facility, does not adequately address the observations. Specifically, more information and details of the corrective actions to address the observations are needed.

Meeting Discussion:

- Adaptimmune acknowledged DMPQ's concerns and will respond by 29 May 2024.

2. Discussion of established Pharmacologic Class

A MAGE-A4-directed genetically modified autologous T cell immunotherapy.

Meeting Discussion:

No discussion during the meeting.

3. Additional Applicant Data

Please refer to Meeting Discussion in 1

4. Information Requests

CMC IR #4 sent May 8, 2024, due May 15, 2024.

Meeting Discussion:

No discussion during the meeting.

5. Risk Management Actions (e.g., REMS, the ability of adverse event reporting and CBER's Sentinel Program to provide sufficient information about product risk)

Currently, a REMS is not anticipated.

Meeting Discussion:

No discussion during the meeting.

6. Postmarketing Requirements/Postmarketing Commitments

Clinical Pharmacology:

You did not assess immunogenicity of afamitresgene autoleucel. There are potential risks of immunogenicity against afamitresgene autoleucel and there is no clinical data to address any potential impact. Therefore, we recommend immunogenicity assessment of afamitresgene autoleucel as postmarketing requirement /postmarketing commitment.

Meeting Discussion:

Adaptimmune does not have a validated assay to perform immunogenicity assessment and will need time to provide the required information. FDA suggested that Adaptimmune should submit revised protocol incorporating immunogenicity assessment in ongoing study. Considering the time needed for immunogenicity assay development and validation, FDA recommended Adaptimmune collect and store samples appropriately for immunogenicity studies at current stage.

OBPV/DPV:

Review of the pharmacovigilance plan and protocol synopsis for the postmarketing long-term follow-up study are ongoing.

Meeting Discussion:

No discussion during the meeting.

7. Major Labeling Issues

Labeling review is ongoing. There are no major labeling issues to discuss at this time.

Meeting Discussion:

No discussion during the meeting.

8. Review Plans

Review of this BLA is ongoing. We will continue sending IRs as necessary to get clarification on any submitted information. FDA plans to send the labeling comments by June 19, 2024.

Meeting Discussion:

No discussion during the meeting.

9. Applicant Questions

Meeting Discussion:

Please refer to discussions 1

10. Wrap-up and Action Items

The Late Cycle Meeting summary will be sent by June 19, 2024

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.