



Our STN: BL 125795/0

**LATE-CYCLE  
MEETING MEMORANDUM**

September 18, 2023

Takeda Pharmaceuticals U.S.A., Inc.  
Attention: Michael Cronin, PharmD  
125 Binney Street  
Cambridge, MA 02142

Dear Dr. Cronin:

Attached is a copy of the memorandum summarizing your August 31, 2023, Late-Cycle 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 the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

If you have any questions, please contact Cara Pardon at (240) 994-8449 or by email at [cara.pardon@fda.hhs.gov](mailto:cara.pardon@fda.hhs.gov).

Sincerely,

Ramani Sista, PhD  
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:** August 31, 2023, 10:30 AM – 12:00 PM, EST.  
**Meeting Location:** via Zoom  
**Application Number:** BLA 125795/0  
**Product Name:** ADAMTS13, recombinant-krhn [ADZYNMA]  
**Proposed Indication:** Prophylactic or on-demand enzyme replacement therapy for patients with congenital thrombotic thrombocytopenic purpura (cTTP)  
**Applicant Name:** Takeda Pharmaceuticals U.S.A., Inc.  
**Meeting Chair:** Nobuko Katagiri, PhD  
**Meeting Recorder:** Cara Pardon, MS

#### **FDA Attendees:**

Esmeralda Alvarado-Facundo, PhD, CBER/OCBQ/DBSQC  
Natalya Ananyeva, PhD, CBER/OTP/OPPT  
Rukmini Bhardwaj, PhD, CBER/OTP/OPT  
Youwei Bi, PhD, CDER/OTS/OCP  
Juliane Carvalho, MS, RAC, CBER/OTP/ORMRR  
Elin Cho, MS, CBER/OBPV/DB  
Muhammad (Umer) Choudhry, MD, CBER/OTP/OCE  
Brianna Davis, CBER/OCBQ/DBSQC  
Selena Daniels, PharmD, PhD, CDER/OND/ODES/DCOA  
Maureen DeMar, RN, CBER/OCBQ/DMPQ  
Heather Erdman, MCPM, RAC, CQPA, CBER/OTP/ORMRR  
Salil Ghosh, MS, PhD, CBER/OCBQ/DBSQC  
Basil Golding, MD, CBER/OTP/OPPT  
Mahmood Farshid, PhD, CBER/OTP/OPPT  
Megha Kaushal, MD, CBER/OTP/OCE  
Hosna Keyvan, CBER/OTP/ORMRR  
Yeowon Kim, MD, CBER/OBPV/DPV  
Lin Huo, PhD, CBER/OBPV/DB  
Katarzyna Jankowska, PhD, CBER/OTP/OPPT  
Jing Ju, PharmD, CDER/OND/ODES/DCOA  
George Kastanis, MS, CBER/OCBQ/DBSQC  
Nobuko Katagiri, PhD, CBER/OTP/OPPT  
Upendra Katneni, PhD, CBER/OTP/OPPT  
Alexey Khrenov, PhD, CBER/OTP/OPPT  
Kristine Khuc, PharmD, CBER/OCBQ/DCM/APLB  
Chava Kimchi-Sarfaty, PhD, CBER/OTP/OPPT  
Linda Le, MBA, CBER/OTP/ORMRR  
Shiowjen Lee, PhD, CBER/OBPV/DB  
Nicole Li, CBER/OCBQ/DMPQ  
Wei Liang, PhD, CBER/OTP  
Jiang Liu, PhD, CDER/OTS/OCP  
Prasad Mathew, MD, CBER/OTP/OCE

Adamma Mba-Jonas, MD, MPH CBER/OBPV/DPV  
Narayan Nair, MD, CBER/OBPV/DPV  
Malcolm Nasirah, PharmD, MS, BCGP, CBER/OCBQ/DIS/BMB  
Cara Pardon, MS, CBER/OTP/ORMRR  
Kenneth Phillips, PhD, CBER/OCBQ/DBSQC  
Carolyn Renshaw, CBER/OCBQ/DMPQ  
Zuben Sauna, PhD, CBER/OTP/OPPT  
John Scott, PhD, MA, CBER/OBPV/DB  
Ramani Sista, PhD, CBER/OTP/ORMRR  
Ila Srivastava, PharmD, CDER/OSE/OMEPRM/DMEPAII  
Theodore Stevens, MS, RAC, CBER/OTP  
Nicole Verdun, MD, CBER/OTP/OCE  
Xiaofei Wang, PhD, CBER/OTP/OCE  
Da Zhang, PhD, CDER/OTS/OCF

**Applicant Attendees:**

Anet Allik, MS, Director, Global Regulatory Lead  
Kayode Badejo, MD, Senior Medical Director, Global Safety Lead  
Jovanna Baptista, MS, Senior Director, Biostatistics  
Jim Blank, PhD, Director, Toxicology  
Michael Cronin, PharmD, Senior Director, Global Regulatory Affairs, Therapeutic Area Lead  
Alicia Jeannotte, MS, Senior Director, Global Regulatory CMC  
Bjorn Mellgard, MD, PhD, Vice President, Global Program Lead  
Becca Nowak, Associate Director, Global Regulatory Project Management and Strategic Planning  
Luying Pan, Head of Bioanalytics, Bioanalytical and Biomarker Sciences and Technologies  
Munjal Patel, PhD, Associate Director, Quantitative Clinical Pharmacology  
Parth Patwari, MD, ScD, Medical Director, Clinical Science  
Pratik Pednekar, Manager, Global Regulatory Affairs, CMC  
Emily Skelton, Senior Manager, Clinical Operations Program Lead  
(b) (6), Pharmaceutical Sciences Lead  
Linda Wang, MD, Executive Medical Director, Global Clinical Development Lead  
Brian Walter, Vice President, Global Regulatory Affairs  
Bella Zhang, MD, PhD, Senior Medical Director, Clinical Science  
Andy Zhu, Senior Director, Global DMPK

**BACKGROUND**

BLA 125795/0 was submitted on March 17, 2023, for ADZYNMA (ADAMTS13, recombinant-krhn).

Proposed indication: Prophylactic or on-demand enzyme replacement therapy for patients with congenital thrombotic thrombocytopenic purpura (cTTP)

PDUFA goal date: November 15, 2023

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on August 21, 2023.

## **DISCUSSION**

### **1. Discussion of Substantive Review Issues (to be continued under item 6)**

#### **a. CMC**

- i. Control of Materials and Critical Steps: Additional (b) (4) of the rADAMTS13 gene from all clinical or commercial campaigns are awaited. An IR will be communicated.

**The Agency confirmed the request for additional available rADAMTS13 (b) (4) results for (b) (4) from all clinical or commercial campaigns.**

**In addition, the Agency confirmed the request to include (b) (4) as part of qualification of new Working Cell Banks, and to extend stability programs for Working Cell Banks and Master Cell Banks to include comprehensive (b) (4) stability testing. The revised versions of qualification protocol and stability programs are expected to be included in Takeda's response.**

**These requests were communicated to Takeda on August 29, 2023 (CMC IR #12).**

**Takeda had no additional questions.**

- ii. Proper name: will be communicated with Takeda at a later stage.

**The Agency confirmed the proper name remains under consideration and will be communicated to Takeda at a later date.**

**Takeda briefly discussed the request for a single INN, as stated in CMC IR #12. Takeda will provide details of their proposal for the single INN which describes the native rADMAMTS13 Q97, apadamase alfa, and asked if the Agency had any further suggestions.**

**The Agency asked Takeda to provide their proposal for a single INN in their response to CMC IR #12 for review by the Agency and will continue negotiations via subsequent IR.**

**Takeda expressed openness to accommodating an informal telecon to discuss a single INN further, if needed.**

2. Established Pharmacologic Class (EPC)

**The Agency confirmed the EPC remains under consideration and would not be discussed in detail at the meeting. If Takeda has their own proposal for EPC, the Agency asked to communicate this proposal via an amendment to the BLA for Agency consideration.**

**Takeda confirmed their proposed EPC for the product would be submitted as an amendment to the BLA for Agency consideration.**

3. Additional Applicant Data

**Takeda confirmed no additional substantive data relating to substantive issues raised or information requests are expected.**

4. Information Requests

- a. DBSQC IR #4, dated August 8, 2023 ( (b) (4) testing)
  - i. Response due September 25, 2023
- b. Clinical Pharmacology/Pharmacometrics IR #6, dated August 16, 2023 (QSP model)
  - ii. Response due August 23, 2023
- c. Clinical Pharmacology/Pharmacometrics IR #7, dated August 16, 2023 (QSP/PK)
  - iii. Response due August 24, 2023

**There was no additional discussion of information requests a-c, as provided in the late-cycle materials.**

**Three additional information requests were communicated after the late-cycle materials were provided to Takeda:**

- d. CMC IR #11, dated August 22
  - i. Response due September 1, 2023, with an extension for question 4 and question 7 granted, due September 7, 2023.
- e. CMC IR #12, dated August 29, 2023
  - i. Response due September 8, 2023
- f. Pharmacovigilance IR #1, dated August 28, 2023
  - i. Response due September 6, 2023

**Takeda confirmed these additional information request responses are on track to be submitted by the requested dates. There was no additional discussion.**

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)

**The Agency confirmed no anticipation for a REMS at this time.**

6. Postmarketing Requirements/Postmarketing Commitments

a. CMC anticipated PMCs:

- i. Process Validation: to run the (b) (4) commercial PPQ validation campaign, perform all validation studies including (b) (4), and report to the Agency as a PMC.

**The Agency stated Takeda agreed to run (b) (4) commercial PPQ (b) (4) campaign and perform all validation studies, in amendment 27, received July 19, 2023. The Agency determined this agreement to be formalized as a PMC and the PMC language will be negotiated and finalized through IR.**

- ii. E/L: to perform analysis of organic leachables from representative Drug Product lots in the ongoing stability study and report these data within annual reports in 2024 and 2025. This is to be formalized as a PMC.

**The Agency stated that in amendment 13, received May 31, 2023, Takeda agreed to perform analysis of organic leachables from representative Drug Product lots in the ongoing stability study and submit the results in the 2024 and 2025 annual reports. The Agency determined this agreement to be formalized as a PMC and the PMC language will be negotiated and finalized through IR.**

- iii. Stability Studies: to develop and validate an extended assessment method for (b) (4) and include this method in the post-approval stability protocol

**The Agency stated that in amendment 33, received August 16, 2023, Takeda agreed to develop and validate an extended assessment method for (b) (4) and include it in the post-stability protocol. The Agency determined this agreement as a PMC and the PMC language will be negotiated and finalized through IR.**

**Takeda asked if the Agency could provide a specific date for communicating the PMC language and the Agency confirmed the language would be communicated soon.**

b. Clinical anticipated PMC:

- iv. Extension study for immunogenicity

**The Agency discussed the clinical PMC which will include a cohort of previously untreated or minimally treated subjects for subgroup analysis of immunogenicity data if feasible.**

**Takeda acknowledged Agency concern about missing information on previously untreated subjects. They stated in the cTTP registry of 130 subjects, inhibitors against ADAMTS13 have not been observed, and the risk of immunogenicity appears to be low. The extension study 3002 is open and able to enroll subjects who have been untreated; one subject with three prior plasma exposures, diagnosed at birth, has been enrolled. Subjects newly presenting with TTP are treated empirically before establishing TTP, and Takeda expects it will be difficult to enroll naïve subjects. A potential scenario would be enrolling newborn siblings of those previously diagnosed. Takeda asked the Agency for comment.**

**The Agency acknowledged Takeda's response and the potential difficulty with collecting information in this cohort. Takeda stated that they will collect information on this population in their extension study.**

- c. Currently, there are no anticipated PMRs

#### **7. Major Labeling Issues**

**The Agency confirmed labeling issues will be communicated and discussed during the labeling negotiations.**

#### **8. Review Plans**

- a. PMRs will be communicated no later than October 4, 2023
- b. PMCs will be communicated no later than October 16, 2023
- c. Label will be sent to Applicant for negotiations no later than October 16, 2023

**The agency confirmed the above review dates for the remainder of the review cycle.**

#### **9. Applicant Questions**

**Takeda had no additional questions.**

#### **10. Wrap-up and Action Items**

**The Agency confirmed the meeting summary will be provided to Takeda within 30 days.**

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.