



Our STN: BL 125795/0

**MID-CYCLE COMMUNICATION  
SUMMARY**  
July 25, 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 summary of your July 14, 2023 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 125795/0 your future submissions related to recombinant ADAMTS13.

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

## Mid-Cycle Communication Teleconference Summary

**Application Type and Number:** BLA 125795/0

**Product Name:** recombinant ADAMTS13 (rADAMTS13)

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

**Applicant:** Takeda Pharmaceuticals U.S.A., Inc.

**Meeting Date & Time:** July 14, 2023, 10:00 AM-11:30 AM ET

**Committee Chair:** Nobuko Katagiri, PhD

**RPM:** Cara Pardon, MS

### FDA Attendees:

Esmeralda Alvarado-Facundo, PhD, CBER/OCBQ/DBSQC

Natalya Ananyeva, PhD, CBER/OTP/OPPT

Danielle Bauman, CBER/OTP/ORMRR

Rukmini Bhardwaj, PhD, CBER/OTP/OPT

Youwei Bi, PhD, CDER/OTS/OCP

Juliane Carvalho, MS, RAC, CBER/OTP/ORMRR

Dennis Cato, CBER/OCBQ/DIS/BMB

Elin Cho, MS, CBER/OBPV/DB

Muhammad (Umer) Choudhry, MD, CBER/OTP/OCE

Heather Erdman, MCPM, RAC, CQPA, CBER/OTP/ORMRR

Megha Kaushal, MD, CBER/OTP/OCE

Salil Ghosh, MS, PhD, CBER/OCBQ/DBSQC

Jiang (Jessica) Hu, PhD, CBER/OBPV/DB

Lin Huo, PhD, CBER/OBPV/DB

Kula Ja, PhD, CBER/OCBQ/DMPQ

Katarzyna Jankowska, PhD, CBER/OTP/OPPT

Kathleen Jones, PhD, CBER/OCBQ/DMPQ

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

Chava Kimchi-Sarfaty, PhD, CBER/OTP/OPPT

Christine Knoll, MD, CBER/OTP/OCE

Wei Liang, PhD, CBER/OTP

Guansheng Liu, PhD, CDER/OTS/OCP

Jiang Liu, PhD, CDER/OTS/OCP

Prasad Mathew, MD, CBER/OTP/OCE

Ashley Munchel, MD, CBER/OTP/OCE

Malcolm Nasirah, PharmD, MS, BCGP, CBER/OCBQ/DIS/BMB

Cara Pardon, MS, CBER/OTP/ORMRR

Lori Peters, CBER/OCBQ/DMPQ

CDR Kenneth Phillips, PhD, CBER/OCBQ/DBSQC

Sandhya Sanduja, PhD, CBER/OTP/OPT

Andrey Sarafanov, PhD, CBER/OTP/OPPT

Zuben Sauna, PhD, CBER/OTP/OPPT  
John Scott, PhD, MA, CBER/OBPV/DB  
Ramani Sista, PhD, CBER/OTP/ORMRR  
Nicole Verdun, MD, CBER/OBRR  
Xiaofei Wang, PhD, CBER/OTP/OCE  
Lihan Yan, PhD, CBER/OBPV/DB  
Da Zhang, PhD, CDER/OTS/OCF  
Iryna Zubkova, PhD, CBER/OCBQ/DMPQ

**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  
Dan Curran, MD, Head, Rare Genetic and Hematology TAU  
Alicia Jeannotte, MS, Senior Director, Global Regulatory CMC  
Chao Li, Associate Director, Global Regulatory Affairs, CMC  
Bjorn Mellgard, MD, PhD, Vice President, Global Program Lead  
Tracy Page, Director, Global Program Management  
Munjal Patel, PhD, Associate Director, Quantitative Clinical Pharmacology  
Emily Skelton, Senior Manager, Clinical Operations Program Lead  
(b) (6), Pharmaceutical Sciences Lead  
Linda Wang, MD, Executive Medical Director, Global Clinical Development Lead  
Bella Zhang, MD, PhD, Senior Medical Director, Clinical Science  
Shan Xiao, PhD, Senior Manager, Statistics

**Discussion Summary:**

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

Meeting Discussion

FDA communicated that CMC deficiencies and questions related to process validation, product quality assurance, and proper naming, will continue to be communicated via information requests.

FDA acknowledged Takeda's commitment to perform Leachables analysis of Drug Product in the ongoing stability study and stated that any additional potential CMC PMCs will be communicated at a later stage of review, but no later than October 16, 2023.

Takeda asked for clarity about proper naming. FDA stated there is an established SOPP and we will communicate any updates or issues through information requests.

2. Information regarding major safety concerns.

Meeting Discussion

FDA stated no major safety concerns have been identified to date and review of the 120-day Safety update, received July 6, 2023, is ongoing. FDA also stated concerns with immunogenicity with subjects who are naïve to this drug product or ADAMTS13 exposure (through receiving plasma infusions), and these concerns will be communicated through information requests.

3. Preliminary Review Committee thinking regarding a) risk management, b) the potential need for any post-marketing requirement(s) (PMRs), and c) the ability of adverse event reporting and CBER's Sentinel Program to provide sufficient information about product risk.

Meeting Discussion

FDA communicated that at this time, the review team has not identified a need for a Risk Evaluation Mitigation Strategy (REMS), post-marketing requirements, or concerns with adverse event reporting.

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

Meeting Discussion

Two pending CMC IRs were communicated:

- i. CMC IR #8 sent on June 29, 2023
  1. Response expected July 19, 2023
- ii. CMC IR #9 sent on June 30, 2023
  1. Response expected July 19, 2023

5. Any new information requests to be communicated.

Meeting Discussion

FDA communicated that as review continues, new information requests will be conveyed as warranted.

6. Proposed date for the Late-Cycle Meeting and the Late-Cycle Meeting Materials:

Meeting Discussion

Takeda was informed of the scheduled late-cycle meeting on August 31, 2023, from 10:30 AM-12:00 PM ET. The Late Cycle Meeting Materials will be provided at least 10 days before the meeting, by August 21, 2023.

Takeda asked if FDA would provide any major requests (outside of CMC concerns), ahead of the late-cycle meeting. FDA confirmed information requests will continue to be sent ahead of the late-cycle meeting.

Noting no major safety concerns have been identified, Takeda asked if FDA could comment on the adequacy of the data. FDA reiterated that the totality of data is under review and FDA will continue to communicate concerns through information requests and substantive concerns will be relayed to Takeda.

7. Updates regarding plans for the AC meeting, if appropriate.

Meeting Discussion

Takeda was informed that an AC meeting is not anticipated.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates, and notification of intent to inspect manufacturing facilities.

Meeting Discussion

FDA communicated that there are no changes to previously communicated dates for the remainder of the review cycle and any changes will be communicated as warranted.

Takeda asked if labeling negotiations could start before October 16, 2023, and FDA confirmed that information requests regarding labeling could be sent before that date, but October 16, 2023, is the deadline for beginning labeling negotiations.

Takeda asked about potential issues with BIMO inspections. FDA confirmed BIMO inspections are ongoing, but no anticipated major sponsor issues are expected.

FDA also confirmed as communicated via email on June 20, 2023, that the manufacturing inspections have been waived.