Food and Drug Administration
Center for Biologics Evaluation and Research
Summary Minutes
77th Cellular, Tissue, and Gene Therapies Advisory Committee Meeting
November 21, 2024

Committee Members
Tabassum (Taby) Ahsan, Ph.D. (Chairperson)
Christopher K., Breuer, M.D. +
Donald B. Kohn, M.D.
Wendy B. London, Ph.D.
Troy Lund, Ph.D., M.D
Sean J. Morrison, Ph.D.
Kathleen O'Sullivan-Fortin, Esq. **
Melanie Ott, M.D., Ph.D.
Nirali N. Shah M.D., M.H.Sc. +
Evan Y. Snyder, M.D., Ph.D.
Cynthia J. Tifft, M.D., Ph.D.
Gil I. Wolfe, M.D.
Joseph Wu, M.D., Ph.D.

Industry Representative Member
Anne-Virginie Eggimann, M.Sc. ***

Alternate Industry Representative
Melissa A. Greenwald, M.D., CAPT USPHS (Ret.) ~ +

Temporary Voting Members
Sanjay P. Ahuja, M.D., M.Sc., M.B.A.
Andrei L. Kindzelski, M.D., Ph.D.
Walter J. Koroshetz, M.D.
Thomas L. Ortel, M.D., Ph.D.
Rajiv Ratan, M.D., Ph.D.

Temporary Voting Member - Patient Representative
Joseph P. O'Brien, M.B.A.

+Not Attending
** Consumer Representative
*** Industry Representative
~Alternate Industry Representative

FDA Participants
Peter W. Marks, M.D., Ph.D.
Nicole Verdun, M.D. (Speaker)
'Lola Fashoyin-Aje, M.D., M.P.H. (Speaker)
Leila P. Hann
Lin Huo, Ph.D.
Karl Kasamon, M.D. (Speaker)
Megha Kaushal, M.D.
Christine Knoll, M.D. (Speaker)
Hairong Shi, Ph.D.

Designated Federal Officer (DFO)
Cicely Reese, Pharm.D., LCDR USPHS

Committee Management Officer (CMO)
Joanna Malsch

Committee Management Specialist (CMS)
Tonica Burke, B.S.

DSAC Director
Prabhakara Atreya Ph.D.

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These summary minutes for the November 21, 2024, meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) were approved on February 7, 2025.

I certify that I participated in the November 21, 2024, meeting of the CTGTAC meeting and that these minutes accurately reflect what transpired.

/s/	/s/
Cicely Reese, Pharm.D., LCDR USPHS, Designated Federal Officer	Tabassum (Taby) Ahsan, Ph.D. Chairperson

On November 21, 2024, the 77th meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) took place in open session to discuss and make recommendations on supplemental biologics license application 125586/546 from AstraZeneca AB, submitted to confirm the clinical benefit of Andexxa (coagulation factor Xa (recombinant), inactivated-zhzo), for patients treated with rivaroxaban or apixaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Given the topic of this meeting, it was determined to be a Particular Matter Involving Specific Parties (PMISP).

On November 21, 2024 at 10:00 a.m. Eastern Daylight Time (EDT), Dr. Tabassum (Taby) Ahsan, Chairperson, called the meeting to order. The DFO, Dr. Cicely Reese, made administrative remarks, conducted roll call, invited the CTGTAC members and consultants to introduce themselves, and read the Conflict of Interest (COI) statement into the public record. There were no conflict-of-interest waivers issued under 18 U.S. Code Section 208 in connection with this meeting. During the open session, the CTGTAC members, consultants, applicant, FDA speakers and staff, and public speakers all participated via Zoom web conference.

Dr. Nicole Verdun, Director, Office of Therapeutic Products, provided FDA Opening Remarks.

Following Opening Remarks, the applicant team of speakers provided presentations entitled:

- Introduction: Jeffy John, M.B.A.
- Burden of Life-Threatening Bleeds Related to FXa Inhibitors and Need to Effective Reversal Agents: Paul A. Nyquist, M.D., M.P.H. Alexis Thompson, M.D., M.P.H.
- Andexanet Efficacy: Per Ladenvall, M.D., Ph.D.
- Andexanet Safety: Rohit Narayan, M.B.Ch.B.
- Clinical Perspective: Ashkan Shoamanesh, M.D., F.R.C.P.C.

- Moderator of Q & A: Matthew Roe, M.D., M.H.S.

Following the applicant presentations, time was allowed for a Question & Answers (Q &A) session between the committee and the applicant team of speakers listed above.

Immediately following the Q &A session, the FDA staff gave a presentation entitled: "sBLA 125586/546".

The FDA speakers were as follows:

Christine Knoll, M.D. and Karl Kasamon, M.D.
Medical Officers
Division of Clinical Evaluation and Hematology
Office of Clinical Evaluation
OTP, CBER, FDA

Following FDA's speaker presentation, time was allowed for a Q &A session from the committee to both FDA speakers, which was followed by a brief lunch break.

Once the committee returned from lunch, a 60-minute Open Public Hearing (OPH) session was held from 1:10 p.m. to 2:10 p.m. ET., in which 13 pre-registered public speakers made oral remarks; some of the pre-registered public speakers also made PowerPoint presentations. The names of OPH speakers and their remarks may be obtained from the transcript posted on the CTGTAC website.

Immediately following the OPH session, there was a brief committee break.

Once the committee returned from the break, the chairperson began the Committee Discussion of the following questions presented to the committee:

1. Primary efficacy endpoint in ANNEXA-I was met, with largest treatment affect from among the 3 endpoint components consisting of the change in the hematoma volume at 12 hours. Other clinically meaningful outcomes (e.g., neurologic status at 24 hours and overall mortality) were not different between the two arms; mRS at Day 30 was worse in the andexanet arm. Discuss whether the treatment effect on the study's primary efficacy endpoint constitutes a clinical benefit to patients.

• Does an effect on hematoma volume change at 12 hours alone constitute clinical benefit?

• Should neurologic status at 24 hours, mRS at Day 30, and overall mortality be incorporated into the assessment of benefit of andexanet?

• Does anti-FXa reduction have a role in the assessment of the benefit of andexanet?

2. ANNEXA-I demonstrated an increased incidence of thrombosis (14.6% versus 6.9%) and thrombosis-related deaths at Day 30 (2.5% versus 0.9%) in the andexanet arm compared to the usual care. Are the serious risks of Andexanet as demonstrated in ANNEXA-I acceptable in the indicated population and in the context of the clinical efficacy demonstrated in ANNEXA-I?

Summary of Discussion:

The Committee agreed that while treatment with Andexxa appears to lead to achievement of hemostatic efficacy at 12 hours, the efficacy data provided did not clearly show a clinically meaningful benefit. The Committee found it challenging to assess the risks of Andexxa (e.g., increased rate of thrombotic events in Andexxa-treated patients) in the context of its current indication, given that ANNEXA-I only evaluated Andexxa in patients with life-threatening intracerebral hemorrhage after receiving oral anticoagulants (apixaban or rivaroxaban). The Committee also expressed uncertainties regarding whether the currently approved Andexxa dosage was optimized for safety as well as effectiveness.

Following the Committee Discussion, Dr. 'Lola Fashoyin-Aje thanked the committee and provided closing remarks.

The committee DFO adjourned the meeting on November 21, 2024, at 3:56 p.m. EDT.

Additional meeting information and details may be obtained from the transcript, which may be viewed at:

Cellular, Tissue, and Gene Therapies Advisory Committee November 21, 2024 Meeting Announcement - 11/21/2024 | FDA.

The recording of the webcast of the meeting may be viewed at:
https://www.youtube.com/live/xztpe5-d9eY