Food and Drug Administration
Center for Biologics Evaluation and Research
Summary Minutes
76th Cellular, Tissue, and Gene Therapies Advisory Committee Meeting
October 31, 2023

Committee Members
Tabassum (Taby) Ahsan, Ph.D. (Acting Chair)
Marshall E. Bloom, M.D. +
Christopher K., Breuer, M.D.
Eric Crombez, M.D. **
Donald B. Kohn, M.D. +
Wendy B. London, Ph.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. +
Gil I. Wolfe, M.D. +
Joseph Wu, M.D., Ph.D.

Temporary Voting Members
Robert A. Dracker, M.D.
Jasmine Hightower, M.S.W.>
Alexis C. Komor, Ph.D.
Lisa Lee, Ph.D.
Amy Shapiro, M.D.
John F. Tisdale, M.D.
Scot A. Wolfe, Ph.D.

Industry Representative
Eric Crombez, M.D. **

Guest Speakers
Daniel Bauer, M.D., Ph.D.
Fyodor Urnov, Ph.D.

FDA Participants
Nicole Verdun, M.D. (Speaker)
Leila P. Hann
Karl Kasamon, M.D. (Speaker)
Komudi Singh, Ph.D. (Speaker)

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

Committee Management Officers (CMO)
LaShawn Marks
Joanne Lipkind, M.S. (Alternate)

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

DSAC Director
Prabhakara Atreya, Ph.D.

+Not Attending
* Consumer Representative
** Industry Representative
>Patient Representative

These summary minutes for the October 31, 2023, meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) were approved on , 2023.

I certify that I participated in the October 31, 2023, meeting of the CTGTAC meeting and that these minutes accurately reflect what transpired.

Food and Drug Administration
Center for Biologics Evaluation and Research
Summary Minutes
76th Cellular, Tissue, and Gene Therapies Advisory Committee Meeting
October 31, 2023

/s/
LCDR Cicely Reese, Pharm.D.
Designated Federal Officer

/s/
Tabassum (Taby) Ahsan, Ph.D.
Acting Chair

On October 31, 2023, the 76th meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) took place in open session to discuss and make recommendations on biologics license application (BLA) 125787 from Vertex Pharmaceuticals, Inc., for exagamglogene autotemcel (exa-cel). The applicant has requested an indication for the treatment of sickle cell disease in patients 12 years and older with recurrent vaso-occlusive crises. Given the topic of this meeting, it was determined to be a Particular Matter Involving Specific Parties (PMISP).

On October 31, 2023 at 9:00 a.m. Eastern Daylight Time (EDT), Dr. Tabassum (Taby) Ahsan, the Acting Chair, 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 was one conflict-of-interest waiver issued under 18 U.S. Code Section 208 in connection with this meeting. During the open session, the CTGTAC members, consultants, applicant, guest speakers, 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, Dr. Fyodor Urnov, Professor, Department of Molecular and Cell Biology, at the University of California, Berkely, and Director of Technology and Translation, Innovative Genomics Institute, Berkeley, California, served as the first of two guest speakers and provided a presentation entitled: “The Scientific Foundations of Human Genome Editing”.

Following the Guest Speaker presentation by Dr. Urnov, Dr. Daniel Bauer, M.D., Ph.D., Staff Physician and Gene Therapy Program Director, Pediatric Hematology-Oncology, Boston Children’s Hospital and the Dana-Farber Cancer Institute, provided a presentation entitled: Comprehensive Evaluation of Genome Editing-Associated Genetic Modifications”.

Following Dr. Bauer’s presentation, time was allowed for questions and answers (Q &A) from the committee to both speakers, which was followed by a brief committee break.

Once the committee returned from break, the applicant team of speakers provided a presentation entitled: “Exa-cel for the Treatment of Sickle Cell Disease (SCD) in Patients ≥ 12 Years With Recurrent Vaso-Occlusive Crises (VOCs)”. The applicant presentations and speakers were as follows:

- Introduction: Stephanie Krogmeier, Ph.D.
- Unmet Need: Alexis Thompson, M.D., M.P.H.
- Efficacy: William Hobbs, M.D., Ph.D.
- Non-Clinical Safety: David Altshuler, M.D., Ph.D.
- Clinical Safety: Christopher Simard, M.D.
- Clinical Perspective: Haydar Frangoul, M.D.

Following the applicant presentations, time was allowed for Q &A session between the committee and the applicant team of speakers listed above, after which, the committee was released for a 45-minute lunch.

Once the committee returned from lunch, a 60-minute Open Public Hearing (OPH) session was held from 12:35 p.m. to 1:35 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.

Following the OPH session, there was a brief committee break. Once the committee returned from the break, FDA staff gave a presentation entitled, "BLA 125787, exagamglogene autotemcel (exa-cel)".

The FDA speakers were as follows:

- Dr. Karl Kasamon, M.D., Reviewer, Office of Clinical Evaluation, Division of Hematology, Benign Hematology Branch, OTP
- Dr. Komudi Singh, Ph.D., Bioinformatics Reviewer, Office of Cellular Therapy and Human Tissue, OTP

Following the FDA speaker presentations, time was allowed for the committee to ask the FDA speakers clarifying questions and receive answers.

Immediately following the FDA speaker presentations, the Chair began the committee discussion portion of the meeting. The committee deliberated on one discussion question asked to the committee:

The following discussion question was presented to the committee:

Please discuss the Applicant's off-target analysis (e.g., in silico and cellular methods) and provide recommendations for additional studies, if needed, to assess the risk of off-target editing for exa-cel.

Summary of Discussion: The committee agreed that the applicant's in silico analysis was detailed with lenient thresholds to generate a list of potential off-target editing sites. With generation of a robust list of off-target edits, the committee suggested that consideration should be given as to which are biologically meaningful. Additional selection criteria for patients may also be appropriate, including pre-screening patients, for example, screening for a CPS1 variant. The committee noted that long-term monitoring of the patients for 15 years is planned but it may be beneficial for additional monitoring to evaluate the edits over real-time and monitoring clonal expansion in treated patients.

Following the committee discussion, Dr. Nicole Verdun thanked the committee and provided closing remarks.

The committee DFO adjourned the meeting on October 31, 2023, at 4:01 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 October 31, 2023 Meeting Announcement - 10/31/2023 | FDA.

The recording of the webcast of the meeting may be viewed at:
https://youtube.com/live/M90IjjxOdQg