Food and Drug Administration
Center for Biologics Evaluation and Research
Summary Minutes
72nd Cellular, Tissue and Gene Therapies Advisory Committee Meeting
June 9-10, 2022

Committee Members Lisa Butterfield, Ph.D. (Chair) Tabassum Ahsan Ph.D. Marshall Bloom, M.D.+ Christopher Breuer, M.D.+ Bernard Fox, Ph.D. Jeannette Yen Lee, Ph.D. Sean Morrison, Ph.D.+ Melanie Ott, Ph.D. Nirali Shah, M.D., MHSc. Gil Wolfe, M.D.+ Joseph Wu, M.D., Ph.D.+ **Temporary Voting Members** Sylvia Anspach, M.S. > (Topic I) John Coffin, Ph.D. (Topic I and II) John DiPersio, Ph.D. (Topic I and II) Amylou Dueck, Ph.D. (Topic I) Victor Gordeuk, M.D. (TNVM Topic I and TVM Topic II) Stephanie Keller, M.D. (Topic I) Jaroslaw Maciejewsi, M.D., Ph.D., F.A.C.P. (Topic I and II) Donna Roberts, M.D., M.S. (Topic I) Steven Shapero, B.S.> (Topic I) Navdeep Singh, Ph.D. > (TNVM Topic I and TVM Topic II) Janelle Trieu, PharmD > (TNVM Topic I and TVM Topic II) **Industry Representative** Eric Crombez, M.D. < (Topic I and II) **Consumer Representative** Randy Hawkins, M.D.** (Topic I and II) +Not Attending ** Alternate Consumer Representative *** Industry Representative <Alternate Industry Representative >Patient Representative	**Speakers and Guest Speakers** Stephen Hughes, Ph.D. NCI (Guest Speaker) **FDA Participants** Melanie Blank, M.D. Wilson Bryan, M.D. Andrew Byrnes, Ph.D. Leah Crisafi, MD., FASA, CDR, USPHS (Speaker) Shelby Elenburg, M.D. (Speaker) Denise Gavin, Ph.D. Elizabeth Hart, M.D. Adnan Jaigirdar, M.D., FACS Karl Kasamon, Ph.D. (Speaker) Anna Kwilas, Ph.D. Peter Marks, M.D., Ph.D. Steven Oh, Ph.D. Tejashri Purohit-Sheth, M.D. Kimberly Schultz, Ph.D. Jakob Reiser, Ph.D. **Designated Federal Officers (DFO)** Christina Vert, M.S. **Committee Management Officer (CMO)** Joanne Lipkind, M.S. **Committee Management Specialist (CMS)** Tonica Burke, B.S. **Director** Prabhakara Atreya, Ph.D.

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These summary minutes for the June 9-10, 2022, meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee were approved on August 4, 2022.

I certify that I participated in the June 9-10, 2022, meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) meeting and that these minutes accurately reflect what transpired.

/S/
Christina Vert, M.S.
Designated Federal Officer

/S/
Lisa H. Butterfield, Ph.D.
Chair

On June 9-10, 2022, at 10:00 a.m. Eastern Daylight Time (EDT), the 73rd meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) took place in open session to discuss two biologics license applications (BLAs) from bluebird bio, Inc.: (1) BLA 125755 for elivaldogene autotemcel to treat patients younger than 18 years of age with early cerebral adrenoleukodystrophy (2) BLA 125717 for betibeglogene autotemcel for the treatment of patients with β-thalassemia who require regular red blood cell transfusions. Given the topic of this meeting, it was determined to be a Particular Matter Involving Specific Parties (PMISP).

On Day 1, June 9, Dr. Lisa Butterfield, the Chair, called the meeting to order. The DFO, Ms. Christina Vert, made administrative remarks, conducted roll call and invited the committee members 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, CTGTAC members, consultants, the Sponsor/Applicant, FDA speakers, Guest Speakers, staff, and the public speakers all participated via the Adobe Connect web conference.

Dr. Wilson Bryan, Director of the Office of Tissues and Advanced Therapies, provided FDA Opening Remarks. This was followed by Session 1: Early CALD Efficacy and Safety.

The Applicant started the session with a set of presentations as listed below:

Ms. Anne-Virginie Eggimann - Introduction

Dr. Florian Eichler - Cerebral Adrenoleukodystrophy

Dr. Jakob Sieker - Efficacy

Dr. Laura Demopoulos - Safety and Benefit/Risk

Dr. Christine Duncan - Clinical Perspective: The Role of eli-cel

Immediately following the Applicant presentation, there was a joint FDA presentation

from Dr. Shelby Elenburg and Dr. Leah Crisafi on "Elivaldogene Autotemcel (Eli-cel): BLA 125755 Clinical Considerations for Efficacy and Specific Safety in Early Cerebral Adrenoleukodystrophy" Following the FDA presentation time was given for Session 1 clarifying questions to presenters.

The Committee was released for a 25- minute lunch. Once the Committee returned from lunch, a 60-minute Open Public Hearing (OPH) session was held from 1:00 p.m. to 2:00 p.m. in which 12 pre-registered public speakers provided presentations. The names of OPH speakers and their remarks may be obtained from the transcript posted on the website.

Following the OPH session the Committee moved into Session 2: Safety, including vector integration. The guest speaker Dr. Stephen Hughes presented on "Integration of HIV Proviruses in Oncogenes Can Cause Clonal Expansion of T Cells and Contribute to the Development of T Cell Lymphomas" The Applicant next presented a set of presentations as listed below:

Ms. Anne-Virginie Eggimann - Introduction

Dr. Melissa Bonner - Lentiviral Vector Safety (relevant to both eli-cel and beti-cel)

Immediately following the Applicant set of presentations, there was a 10 -minute break.

Following the break, an FDA presentation was given by Dr. Leah Crisafi on "Risk of Insertional Oncogenesis with Eli-cel, Lovo-cel, and Beti-cel". Following the FDA presentation, time was given for Session 2 clarifying questions to presenters.

The Committee then started Session 3: Early CALD Discussion and Voting

The following discussion and voting questions were presented to the Committee:

Day 1 Questions for BLA 125755

Discussion Questions

1. The eli-cel efficacy data are difficult to interpret due to problems with the benchmark calculation, issues of comparability between populations, potential bias, concerns regarding imputation methods, few events during a limited duration of follow-up, and limited sample size for treatment and control populations.

a. Please discuss the limitations of the primary and secondary efficacy endpoint data, and whether the data support the presence of a clinically meaningful benefit of eli-cel.

b. Please discuss the population(s) (e.g., children without a matched and willing sibling donor, children without a matched donor) in which the efficacy data are, or are not, supportive of a clinically meaningful benefit.

Summary of Discussion: *The committee agreed that there are limitations to the efficacy data, but that the data supports the efficacy of eli-cel in boys without a matched donor. Some members of the committee indicated that the data were sufficient to support the use of eli-cel to treat patients with a matched unrelated donor. The committee thought that a 24-month time period for the primary efficacy endpoint was appropriate. That analysis should be ongoing for patients receiving eli-cel and compared against patients receiving a bone-marrow transplant, to assess the relative benefit-risk profile of the two treatment options.*

2. Three eli-cel-treated subjects have developed myelodysplastic syndrome (MDS). Subjects with sickle cell disease treated with a related product, lovotibeglogene autotemcel (lovo-cel), have been diagnosed with myeloid malignancies. Please discuss the extent to which the myeloid malignancies associated with lovo-cel raise concerns regarding risk for hematologic malignancy with eli-cel.

Summary of Discussion: *The committee's opinion was that lovo-cel and eli-cel are substantially different, such that the lovo-cel data should not negatively impact the eli-cel safety analysis.*

3. Eli-cel has a risk of hematologic malignancy, a potentially fatal adverse event. The number of cases of malignancy (currently 3/67, or 4%) seems likely to increase over time. In addition to the three recognized cases of MDS, there are at least four other subjects with concern for impending MDS. Although the clinical significance is unclear, 98% of subjects in the eli-cel study population have vector integration sites in MECOM, a proto-oncogene. Please discuss the risk of insertional oncogenesis in patients with early active childhood cerebral adrenoleukodystrophy (CALD) treated with eli-cel.

Summary of Discussion: *The committee acknowledged the risk of MDS for patients treated with eli-cel, and the likelihood of more cases of hematologic malignancy being diagnosed over time. The committee expressed concerns that available data of MDS in pediatric patients may not inform prognosis in patients developing MDS after receiving eli-cel, because malignancies that result from insertional oncogenesis may behave differently than spontaneously arising MDS, and because the only cure for MDS is hematopoietic stem cell transplant, for which matched donor options would be limited in the eli-cel patient population. However, given the current risks of graft-versus-host disease (GvHD) and untreated CALD disease, the overall benefit-risk profile of eli-cel is favorable. The committee agreed with the need for continued close monitoring and*

detailed surveillance, including sequence analysis of integration sites, bone marrow biopsies to identify MDS, and early intervention for cases of MDS. The committee also recommended that the Applicant perform additional mechanistic studies to understand why MDS occurred following eli-cel treatment. The committee also recommended that if the product is approved, that FDA continue to assess the benefit-risk of eli-cel treatment in the future, with consideration of any additional cases of malignancy and the outcomes for those who develop malignancy.

Voting Questions for BLA 125755

1. Are the lovo-cel safety data relevant to the safety assessment of eli-cel?

The results of the vote were as follows: Yes=1; No=13; Abstain=1.

2. Do the benefits of eli-cel outweigh the risks, for the treatment of any sub-population of children with early active cerebral adrenoleukodystrophy (CALD)?

The results of the vote were as follows: Yes=15; No=0; Abstain=0.

When explaining your vote for Question 2:

a. For Committee members who voted yes, please include discussion of the following:

i. The sub-population(s) of children with early active CALD for whom you believe there is a favorable benefit-risk profile.

ii. Any additional information you consider necessary to support a favorable benefit-risk profile in any other CALD sub-population.

iii. Your recommendations, if any, for risk monitoring and mitigation for patients with CALD who receive eli-cel.

b. For Committee members who voted no, please include discussion of the following:

i. Any additional information you consider necessary to support a favorable benefit-risk profile in a particular CALD sub-population.

ii. Your recommendations, if any, for risk monitoring and mitigation for patients with CALD who receive eli-cel.

Following the vote, the Chair asked that all voting members provide an explanation for their individual voting decisions, which they provided.

After the Committee Discussion of Questions and Voting, Dr. Wilson Bryan, provided closing remarks.

Dr. Lisa Butterfield then handed the meeting over to the DFO who adjourned the meeting on June 9, 2022, at 6:05 PM EDT.

Day 2 Minutes

On June 10, 2022, at 10:00 a.m. Eastern Daylight Time (EDT), the 73rd meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) took place in open session to discuss bluebird bio, Inc. BLA 125717 for betibeglogene autotemcel for the treatment of patients with β-thalassemia who require regular red blood cell transfusions.

On Day 2, June 10, Dr. Lisa Butterfield, the Chair, called the meeting to order. The DFO, Ms. Christina Vert, made administrative remarks, conducted roll call and invited the committee members 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, CTGTAC members, consultants, Sponsor/Applicant, FDA speakers, Guest Speakers, staff, and the public speakers all participated via the Adobe Connect web conference.

Dr. Wilson Bryan, Director of the Office of Tissues and Advanced Therapies, provided FDA Opening Remarks. This was followed by Session 4: beta-thalassemia Efficacy and Safety. The Applicant started the session with a set of presentations as listed below:

Ms. Anne-Virginie Eggimann - Introduction
Dr. Sujit Sheth - Unmet Medical Need
Dr. Rich Colvin - Efficacy
Dr. Ajay Singh - Safety
Dr. Alexis Thompson – Benefit-Risk

Immediately following the Applicant presentation, there was a FDA presentation by Dr. Karl Kasamon "BLA 125717 betibeglogene autotemcel (beti-cel) treatment of patients with

β-thalassemia who require regular red blood cell (RBC) transfusions". Following the FDA presentation time was given for Session 4 clarifying questions to presenters.

The committee was released for a 35-minute lunch break. Once the Committee returned from lunch break, a 60-minute Open Public Hearing (OPH) session was held from 1:00 p.m. to 2:00 p.m. in which 12 pre-registered public speakers made presentations. The names of OPH speakers and their remarks may be obtained from the transcript posted on the website. Following the OPH session there was a Committee Discussion of Questions session with Committee Members and Temporary Voting Members.

The Committee then started Session 5: beta-thalassemia Discussion and Voting

The following discussion and voting questions were presented to the Committee:

Day 2 Questions for BLA 125717

Discussion Questions

1. Hematologic malignancies have not occurred in transfusion-dependent β-thalassemia (TDT) subjects treated with beti-cel. However, the beti-cel lentiviral vector (LVV) is similar to the vector used in sickle cell disease (SCD) and is related to the vector used for cerebral adrenoleukodystrophy (CALD), and there have been cases of hematologic malignancies in both SCD and CALD subjects in other studies. In this setting, what is the likelihood that the constellation of delayed platelet reconstitution, abnormal marrow morphology findings, and insertion site analyses will predict future development of hematologic malignancies in TDT patients treated with beti-cel?

Summary of Discussion: *In their discussion, committee members highlighted the substantial differences between products, vectors, and disease states, as well as absence of any evidence of insertional oncogenesis to date with beti-cel. The committee reached agreement that while the etiology and significance of delayed hematopoietic reconstitution and cytopenias in beti-cel recipients is unclear, the differences between beti-cel versus eli-cel, as well as the underlying pathophysiology of beta-thalassemia vs. SCD and CALD, lessen their concern of hematologic malignancy risk in patients with beta-thalassemia.*

2. Please discuss whether patients with TDT should be screened for potential germline and somatic mutations predisposing to hematologic malignancy prior to administration of beti-cel. What screening tests, if any, for such mutations would you

recommend?

Summary of Discussion: *The majority of the panel generally did not recommend screening for germline somatic mutations prior to product administration. A suggestion was to evaluate subclone evolution with next-generation sequencing (NGS), although a sensitivity of 0.2-0.5 percent would be needed, and such high sensitivity may not be feasible with available panels. Another recommendation involved (in addition to germline/somatic mutation evaluation), baseline bone marrow testing with standard cytogenetics before treatment, to be subsequently reassessed in the event of cytopenias.*

3. Please discuss the adequacy of the proposed postmarketing pharmacovigilance program, including the long-term follow-up study and registry study and discuss additional recommendations for safety monitoring for hematologic malignancies.

Summary of Discussion: *The committee was unable to reach a consensus regarding multiple different safety monitoring recommendations. Assays discussed included detailed phenotyping to include more rare sub-clones, differentiating between original and expanded products, as well as baseline cells before and after transduction. Also mentioned was bone marrow analysis at baseline and possibly when primary endpoints related to neutrophil and platelet engraftments are not reached.*

4. Please discuss recommendations for specific testing for hematologic malignancies following administration of beti-cel, to include frequency of testing, in patients with TDT.

Summary of Discussion: *The panel mentioned tracking the importance of percent transduction efficiency, tracking the integration sites, clonal hematopoiesis in subclones and primitive stem cells, as well as NGS for driver mutations and consideration of FISH for its greater sensitivity. Some committee members also mentioned performing pre-implantation integration site analysis on a small sample of CD34+ drug product cells to later determine if the frequencies of specific gene integration events have increased relative to what was transplanted.*

Voting Question for BLA 125717

1. Do the benefits of beti-cel outweigh the risks for the treatment of subjects with transfusion-dependent β-thalassemia?

The results of the vote were as follows: Yes=13; No=0; Abstain=0.

When explaining your vote:

a. For Committee members who voted yes, please include discussion of your recommendations, if any, for risk monitoring and mitigation for patients who receive beti-cel for treatment of TDT.

b. For Committee members who voted no, please discuss the following:

i. Any additional information you consider necessary to support a favorable benefit-risk profile.

ii. Your recommendations, if any, for risk monitoring and mitigation for patients who receive beti-cel for treatment of TDT.

Following the vote, the Chair asked that all voting members provide an explanation for their individual voting decisions, which they provided.

After the Committee Discussion of Questions, Dr. Peter Marks, Director of the Center for Biologics Evaluation and Research, provided closing remarks.

Dr. Lisa Butterfield handed the meeting over to the DFO who adjourned the meeting on June 10, 2022, at 3:15 PM EDT.

Additional information and details may be obtained from the transcript and the recording of the webcast of the meeting may be viewed at:
https://www.fda.gov/advisory-committees/advisory-committee-calendar/cellular-tissue-and-gene-therapies-advisory-committee-june-9-10-2022-meeting-announcement-06092022

Direct Link to Recording of the Open Session:

- Day 1 June 9 link: https://youtu.be/RvtTK3KNl5g
- Day 2 June 10 link: https://youtu.be/Eo2BXnGienc