



Our STN: BL 125755

**LATE-CYCLE  
MEETING MEMORANDUM**

bluebird bio, Inc.  
Attention: Denise Schultz, MS  
Director, Regulatory CMC  
455 Grand Union Boulevard  
Somerville, MA 02145

Dear Ms. Schultz:

Attached is a copy of the memorandum summarizing your May 31, 2022 Late-Cycle Meeting teleconference with CBER. This memorandum constitutes the official record of the meeting teleconference. If your understanding of the meeting 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 the Regulatory Project Managers, Colleen Caldwell and Julia Wright, at [Colleen.Caldwell@fda.hhs.gov](mailto:Colleen.Caldwell@fda.hhs.gov) and [Julia.Wright@fda.hhs.gov](mailto:Julia.Wright@fda.hhs.gov).

Sincerely,

Steven S. Oh, PhD  
Acting Director  
Division of Cellular and Gene Therapies  
Office of Tissues and Advanced Therapies  
Center for Biologics Evaluation and Research

### **Late-Cycle Meeting Summary**

**Meeting Date and Time:** May 31, 2022 3:00pm – 4:30pm ET  
**Meeting Location:** via ZoomGov (Teleconference)

**Application Number:** BLA 125755  
**Product Name:** elivaldogene autotemcel  
**Proposed Indication:** Treatment of patients less than 18 years of age with early cerebral adrenoleukodystrophy who do not have an available and willing HLA-matched sibling HSC donor

**Applicant Name:** bluebird bio, Inc.  
**Meeting Chair:** Anna Kwilas, PhD  
**Meeting Recorder:** Julia Wright and Colleen Caldwell

### **FDA ATTENDEES**

Meghna Alimchandani, MD, CBER/OBPV/DPV  
Esmeralda Alvarado Facundo, PhD, CBER/OCBQ/DBSQC  
Mona Badawy, CBER/OTAT/DRPM  
Kimberly Benton, PhD, CBER/OTAT  
Melanie Blank, MD, CBER/OTAT/DCEPT  
Danielle Brooks, PhD, CBER/OTAT/DCEPT  
Wilson W. Bryan, MD, CBER/OTAT  
Colleen Caldwell, MS, MPH, CBER/OTAT/DRPM  
Dennis Cato, CBER/OCBQ/DIS/BMB  
Cecilia Crowley, CBER/OTAT/DRPM  
Benjamin Cyge, CBER/OCBQ/DCM/APLB  
Shelby Elenburg, MD, CBER/OTAT/DCEPT  
Alyssa Kosmides Galaro, PhD, CBER/OTAT/DCEPT  
Denise Gavin, PhD, CBER/OTAT/DCGT  
Leila Hann, CBER/OTAT  
Elizabeth Hart, MD, CBER/OTAT/DCEPT  
Lin Huo, PhD, CBER/OBPV/DB  
Adnan Jaigirdar, MD, FACS, CBER/OTAT/DCEPT  
Beatrice Kallungal, MS, CBER/OTAT/DRPM  
Colonious King, CBER/OCBQ/DIS  
Alyssa Kitchel, PhD, CBER/OTAT/DCGT  
Anna Kwilas, PhD, CBER/OTAT/DCGT  
Wei Liang, PhD, CBER/OTAT  
Shuya (Joshua) Lu, PhD, CBER/OBPV  
Carrie Mampilly, CBER/OCBQ/DIS  
Tyree Newman, MDiv, CBER/OTAT/DRPM  
Manette Niu, MD, CBER/OBPV  
Steven Oh, PhD, CBER/OTAT/DCGT  
Tao Pan, PhD, CBER/OCBQ/DBSQC

Cara Pardon, MS, CBER/OTAT/DRPM  
Most Parvin, CBER/OCBQ/DBSQC/LBVI  
Lori Peters, CBER/OCBQ/DMPQ  
Tejashri Purohit-Sheth, MD, CBER/OTAT/DCEPT  
Jakob Reiser, PhD, CBER/OTAT/DCGT  
Laura Ricles, PhD, CBER/OTAT/DCGT  
Sonny Saini, CBER/OCBQ/DCM/APLB  
Helen Sansone, CBER/OTAT/DRPM  
Seth Schulte, CBER/OCBQ/DBSQC  
Kimberly Schultz, PhD, CBER/OTAT/DCGT  
John Scott, PhD, CBER/OBPV/DB  
Muhammad Shahabuddin, CBER/OCBQ/DBSQC/LBVI  
Shalini Seetharaman, CBER/OTAT/DRPM  
Ramani Sista, PhD, CBER/OTAT/DRPM  
Brian Stultz, MS, CBER/OTAT/DCGT  
Alisha Thomas, MD, MPH, CBER/OBPV  
Edward Thompson, CBER/OTAT/DRPM  
Andrew Timmons, PhD, CBER/OTAT/DCGT  
Lori Tull, CBER/OTAT/DRPM  
Xiaofei Wang, PhD, CBER/OTAT/DCEPT  
Wei Wang, PhD, CBER/OCBQ/DMPQ  
Julia Wright, MHA, RN, CBER/OTAT/DRPM

#### **APPLICANT ATTENDEES**

Ajay Singh, MD, Vice President, Pharmacovigilance  
Anne-Virginie Eggimann, MSc, Chief Regulatory Officer  
Bem Atsma, Director, Regulatory Science – CMC  
Denise Schultz, Director, Regulatory Science – CMC  
Drew O'Brien, Senior Director, Quality Control  
Frederic Prince, PhD, Vice President, Program Lead eli-cel  
Geoff Parsons, PhD, Senior Director, Research  
Himal Thakar, MD, Vice President, Head of Clinical Research  
Jakob Sieker, MD, Senior Medical Director, Clinical Research Development  
Julie Batal, Vice President, Regulatory Labeling, Advertising and Promotion  
Kelly Kral, Senior Director, Process Development  
Laura Demopoulos, MD, Vice President, Pharmacovigilance  
Leslie Wilder, MS, Vice President, Regulatory Science – CMC  
Lin Pan, MS, Director, Biostatistics  
Nick Keener, Vice President, Manufacturing Operations  
Nicole Floro, MS, Senior Director, Pharmacovigilance  
Rachel Chevalier, Associate Director, Quality Control  
Richard Colvin, MD, Chief Medical Officer  
Sarah Scott, PharmD, Associate Director, Regulatory Science  
(b) (4) , PharmD, Senior Consultant, Regulatory Science

## **BACKGROUND**

BLA 125755 was submitted on October 18, 2021, for elivaldogene autotemcel.

Proposed indication: Treatment of patients less than 18 years of age with early cerebral adrenoleukodystrophy who do not have an available and willing HLA-matched sibling HSC donor

PDUFA goal date: September 16, 2022

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on May 20, 2022 and issued Advisory Committee Briefing Materials on May 12, 2022.

## DISCUSSION

### 1. Discussion of Substantive Review Issues

#### a. Chemistry, Manufacturing, and Controls

- i. A lack of Drug Product lot release analytical method robustness assessment as described in CMC IR #23 provided to the Applicant on May 13, 2022.
- ii. The testing of the final container closure ( (b) (4) -cryobag) is incomplete as provided to date. In CMC IR #23 provided to the Applicant on May 13, 2022, the Applicant was asked to provide all the relevant testing performed by the (b) (4) manufacturer and a timeline for the testing that they are responsible for and have not performed to date.

#### **Meeting Discussion:**

FDA noted the Agency would further discuss these CMC issues later in the meeting if time allowed.

#### b. **Clinical:** All clinical issues were highlighted in the draft Advisory Committee briefing document, provided to the Applicant on May 12, 2022.

1. The benchmark calculation that was used for the primary efficacy analysis was based on data from populations that were not comparable to the eli-cel population at baseline (i.e., “the early active disease population”). There were a multitude of problems with the benchmark calculation that made the primary efficacy analysis uninterpretable.
2. Because the studies were open-label, the identification of an MFD primary endpoint event may have been susceptible to the introduction of bias.
3. The principal comparator allo-HSCT data in Study ALD-103 were partially collected retrospectively. Retrospective data collection can introduce bias.
4. The subjects in Study ALD-103 were somewhat older and had higher Loes scores (a prognostic biomarker) than the eli-cel population, raising concerns about comparability.
5. The repeat HSCT events done for graft failure (not CALD progression) in ALD-103 were imputed as failure of MFD-free survival in the Applicant’s original K-M analyses, biasing the results in favor of eli-cel.
6. Subjects in Studies ALD-102 and ALD-103 had a relatively stable course (few endpoint events). This stability might be expected in a population of patients with CALD during an early or preclinical stage of their disease (even in the absence of any treatment). This, combined with paucity of data beyond 2

years of observation limit efficacy data interpretability in the externally controlled study.

7. Although the efficacy of eli-cel looked similar to the efficacy of HSCT in the K-M analysis, it has not been demonstrated that HSCT is more effective than no treatment in the early active disease population. Therefore, comparability to HSCT may not translate to superiority to no treatment in this early active disease population over a 2-year period following diagnosis.
8. When pooling subjects in Studies ALD-101 and ALD-103, the HLA-unmatched HSCT population appears to have a worse prognosis compared to HLA-matched HSCT and eli-cel, with a high early death rate. The biological plausibility of a “real” difference in prognosis between an unmatched and a matched HSCT population must be weighed against the uncertainty related to having few subjects in the unmatched HSCT subgroup (n=17).
9. Eli-cel has a risk of hematologic malignancy, a potentially fatal adverse event. The number of cases of malignancy (currently 3/67, or 4.4%) seems likely to increase over time. There are at least three cases with concern for impending MDS in addition to the three recognized cases of MDS. In the MDS cases, there is recurrent viral integration into the *MECOM* locus with EVI1 overexpression, and persistent cytopenias and/or clonal expansion in other subjects.
10. In addition to the occurrence of MDS in eli-cel-treated subjects, there have been diagnoses of myeloid malignancies after administration of a related product, lovo-cel, to subjects with sickle cell disease.

**Meeting Discussion:**

Applicant acknowledged FDA’s position and will address issues at the upcoming Advisory Committee Meeting. Applicant reiterated their position that there is a positive benefit-risk profile for subjects with no sibling-matched donor.

2. Additional Applicant Data

There was no discussion of additional data at the meeting.

3. Information Requests

- a. Clinical Pharmacology (IR#22), sent May 8, 2022; response due May 23, 2022

**Meeting Discussion:**

FDA noted the response to this Information Request was received by the Agency.

#### 4. Discussion of Upcoming Advisory Committee Meeting

**Meeting Discussion:**

Applicant acknowledged that the Agency's position is that there may be a favorable benefit/risk profile in the CALD population without a prospective matched donor. The Applicant voiced their preference that the Agency focus on the MUD population separately from the unmatched donor population when asking the Advisory Committee if about benefit/ risk in subpopulations. Applicant asked if the AC Agenda would be made available prior to June 7, 2022, and FDA confirmed the agenda, questions and roster will be posted by June 7, 2022.

#### 5. Risk Management Actions (e.g., REMS)

- FDA is currently still reviewing the data and having internal discussions on risk mitigation strategies, and we anticipate the AC meeting will provide additional insight that will be considered in this regard.

#### 6. Postmarketing Requirements/Postmarketing Commitments

- The review is currently ongoing

#### 7. Major Labeling Issues

- No major labeling issues have been identified at this time. The labeling review is ongoing.

**Meeting Discussion:**

Applicant stated they plan to follow eli-cel treated patients with routine CBCs every 6 months after eli-cel treatment. Applicant further stated that, to avoid confusion, and to ensure that the patients treated with eli-cel are those at highest risk of CALD progression, they propose to modify the population in the indication statement to "with early and active CALD."

FDA acknowledged Applicant's proposals and the Agency stated that this will be discussed further during the interactive label review.

#### 8. Review Plans

- Label will be sent to Applicant for negotiations by August 18, 2022

#### 9. Applicant Questions

**Meeting Discussion:**

Applicant asked if the Agency had reviewed the CMC IR responses recently submitted and asked for Agency comment on analytical robustness as well as remaining issues regarding the DP container closure system.

FDA confirmed the Agency is still in the process of reviewing the container closure information and cannot provide any comments at this time.

FDA confirmed the Agency reviewed the robustness data. FDA wants to ensure that the Applicant's plans for future robustness data is in line with the Agency's expectations. FDA further stated that another information request will be sent, and the Agency will ask for an outline of the planned analytical robustness testing and may communicate with the applicant through additional information requests and/or informal telecon(s) to gain alignment on the plans.

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

**Meeting Discussion:**

FDA stated applicant will receive the Late Cycle Meeting Summary within 30 days, and applicant provided their understanding of the meeting discussion.

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.