



Our STN: BLA 125717/0

**LATE-CYCLE**  
**MEETING MEMORANDUM**  
June 6, 2022

bluebird bio, Inc.  
Attention: Eleanor Yu, PharmD  
455 Grand Union Blvd  
Somerville, MA 02145

Dear Dr. Yu:

Attached is a copy of the memorandum summarizing your May 23, 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 Cara Pardon and Mona Badawy at [cara.pardon@fda.hhs.gov](mailto:cara.pardon@fda.hhs.gov) and [mona.badawy@fda.hhs.gov](mailto:mona.badawy@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 23, 2022 from 12:30-2:00 PM  
**Meeting Location:** teleconference

**Application Number:** BLA 125717/0  
**Product Name:** betibeglogene autotemcel [ZYNTEGLO]  
**Proposed Indications:** Treatment of patients with  $\beta$ -thalassemia who require regular red blood cell (RBC) transfusions  
**Applicant Name:** bluebird bio, Inc.

**Meeting Chair:** Jakob Reiser, PhD  
**Meeting Recorder:** Cara Pardon, MS and Mona Badawy

### **FDA ATTENDEES**

Meghna Alimchandani, MD, CBER/OBPV/DPV  
Firoozeh Alvandi, MD, CBER/OBPV/DPV/PB  
Esmeralda Alvarado Facundo, PhD, CBER/OCBQ/DBSQC  
Rachael Anatol, PhD, CBER/OTAT  
Mona Badawy, CBER/OTAT/DRPM  
Kimberly Benton, PhD, CBER/OTAT  
Wilson W. Bryan, MD, CBER/OTAT  
Colleen Caldwell, MS, MPH, CBER/OTAT/DRPM  
David Cantu, PhD, CBER/OTAT/DCEPT  
Juliane Carvalho, MS, RAC, CBER/OTAT/DRPM  
Dennis Cato, CBER/OCBQ/DIS  
Benjamin Cyge, CBER/OCBQ/DCM/APLB  
Chaohong Fan, MD, PhD, CBER/OTAT/DCEPT  
Zhaoba Fan, PhD, CDRH/OSEL  
Varsha Garnepudi, PhD, CBER/OCBQ/DBSQC  
Denise Gavin, PhD, CBER/OTAT/DCGT  
Leila Hann, CBER/OTAT  
Andrew Harmon, PhD, CBER/OTAT/DCGT  
Jie He, CBER/OCBQ/DMPQ  
Jiang Hu, PhD, CBER/OBPV/DB  
Lin Huo, PhD, CBER/OBPV/DB  
Adnan Jaigirdar, MD, FACS, CBER/OTAT/DCEPT  
Karl Kasamon, MD, CBER/OTAT/DCEPT  
Kristine Khuc, PharmD, CBER/OCBQ/DCM/APLB  
Colonious King, CBER/OCBQ/DIS  
Alyssa Kitchel, PhD, CBER/OTAT/DCGT  
Anna Kwilas, PhD, CBER/OTAT/DCGT  
Carolyn Laurencot, PhD, CBER/OTAT/DCGT  
Sarah Lee, CBER/OCBQ/DMPQ  
Wei Liang, PhD, CBER/OTAT  
Tiffany Lucas, PhD, CBER/OTAT/DCGT

Adamma Mba-Jonas, MD, MPH CBER/OBPV/DPV/PB  
Leyish Minie, MSN, RN, CBER/OTAT/DRPM  
Bao-Ngoc Nguyen, PhD, CBER/OTAT  
Steven Oh, PhD, CBER/OTAT/DCGT  
Tao Pan, PhD, CBER/OCBQ/DBSQC  
Cara Pardon, MS, CBER/OTAT/DRPM  
Lori Peters, CBER/OCBQ/DMPQ  
Caroline Pinto, PhD, CDRH/OSEL  
Jakob Reiser, PhD, CBER/OTAT/DCGT  
Laura Ricles, PhD, CBER/OTAT/DCGT  
Tal Salz, PhD, CBER/OTAT/DCGT  
Sandhya Sanduja, PhD, CBER/OTAT/DCEPT  
Kimberly Schultz, PhD, CBER/OTAT/DCGT  
John Scott, PhD, CBER/OBPV/DB  
Ramani Sista, PhD, CBER/OTAT/DRPM  
Lisa Stockbridge, PhD, CBER/OCBQ/DCM/APLB  
Melek Sunay, PhD, CBER/OTAT/DCEPT  
Edward Thompson, CBER/OTAT/DRPM  
Andrew Timmons, PhD, CBER/OTAT/DCGT  
Lori Tull, CBER/OTAT/DRPM  
Wei Wang, PhD, CBER/OCBQ/DMPQ  
Xiaofei Wang, PhD, CBER/OTAT/DCEPT  
Claire Wernly, CBER/OCBQ/DBSQC  
Julia Wright, MHA, RN, CBER/OTAT/DRPM  
Lihan Yan, PhD, CBER/DBPV/DB

#### **APPLICANT ATTENDEES**

Melissa Bonner, PhD - Research, Senior Vice President  
Richard Colvin, MD, PhD - Clinical Development, Chief Medical Officer  
Anne-Virginie Eggimann, MSc - Regulatory, Chief Regulatory Officer  
Nick Keener, PhD - Manufacturing Operations, Vice President  
Kelly Kral, MS - CMC Strategy and Operations, Senior Director  
Helena Madden, PhD - Regulatory Science - CMC, Senior Director  
Drew O'Brien, MSc, Senior Director, Quality Control  
Aashita Parikh, MS - Regulatory Science, Director  
Ajay Singh, MD - Pharmacovigilance, Vice President  
Gloria Tao, PhD - Biostatistics, Director  
Himal Thakar, MD - Clinical Development, Senior Director  
Leslie Wilder, MS - Regulatory Science - CMC, Vice President  
Eleanor Yu, PharmD - Regulatory Science, Senior Director

## **BACKGROUND**

BLA 125717/0 for betibeglogene autotemcel was submitted on September 20, 2022.

Proposed indication: Treatment of patients with  $\beta$ -thalassemia who require regular red blood cell (RBC) transfusions

PDUFA goal date: August 19, 2022

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on May 13, 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 #5 provided to the Applicant on May 13, 2022.

FDA confirmed receipt of CMC IR #5 responses. Additional time is needed to review the responses, and any additional information needed will be conveyed, as applicable. Bluebird confirmed availability for further informal discussion, if needed.

- ii. An agreement on leachable testing for the cell manufacturing bag. Discussions with applicant regarding leachable testing will continue through IRs until a final agreement is reached.

FDA confirmed that review of the leachable testing is ongoing and that information requests will continue as needed, to reach an agreement.

- iii. Stability (shelf life) of BB305 LVV. Only data up to the (b) (4) time point is available for vector lots generated with the commercial manufacturing process as discussed in CMC IR #5 provided to the Applicant on May 13, 2022.

FDA confirmed stability data for BB305 LVV was provided in response to CMC IR #4 and is under review.

- iv. (b) (4) Cryobag bag

- i. Integrity during freeze/thaw
- ii. Suspension (hanger eyelet) testing to show that the container closure is safe when used as intended.
- iii. Results from sensitization and hemocompatibility testing
- iv. Endotoxin acceptance criterion specification
- v. Toxicological risk for (b) (4) in the (b) (4) bag extract

Bluebird asked if FDA could provide a timeline for response to their leachable study plans provided in their CMC IR #5 response, which includes results to be provided after the action due date. FDA confirmed that review of CMC IR #5 responses is ongoing and could not comment on the proposal.

FDA DMPQ team asked about bluebird's timeline for changing the container closure integrity test method from (b) (4) method to a more sensitive (b) (4) method. Bluebird confirmed that the new method is still under development and did not provide a timeline for implementation. FDA confirmed an IR may be sent to request further details regarding the implementation timeline.

b. Clinical

- i. The FDA outlined the following key safety concerns: constellation of frequently delayed and incomplete platelet reconstitution, a number of marrow abnormalities, oligoclonal LVV integrations (including into proto-oncogenes) and VAMP4 gene LVV integrations in 56% of subjects with TDT. These findings are particularly concerning because one of two sickle cell disease (SCD) subjects with acute myeloid leukemia (AML) after treatment with lovo-cel had a predominant clone with VAMP4 gene integration, though causality has not been established, and other recipients of lovo-cel developed syndromes which are being evaluated for MDS. Furthermore, three cases of MDS with predominant clones into MECOM and PRDM16 oncogenes have been reported after treatment with eli-cel for cerebral adrenoleukodystrophy (CALD).

Bluebird provided a summary of safety topics which they plan to present at the upcoming Advisory Committee (AC) meeting. FDA acknowledged the topics outlined were reasonable.

Bluebird provided further information regarding the oncogenicity of VAMP4 and asked if there were any data they could provide the FDA. Bluebird also asked if there were any follow-up questions regarding the HGB-207 and HGB-212 independently-read bone marrow reports.

FDA clarified that this matter regarding adequacy of Applicant's response on potential contribution of VAMP4 gene LVV integration in the AML case reported in the SCD subject is still under review. FDA did not have any specific questions or comments for the pathologists pertaining to the marrow review.

Furthermore, given the complexity of the above safety concerns, FDA indicated the BLA will be presented at Advisory Committee for discussion on benefit-risk in this population and risk mitigation recommendations.

- ii. Bluebird asked why HGB-205 data was not included in the safety and efficacy data in the AC briefing document, and would this study be included in the label.

FDA clarified that HGB-205 data were not included in analysis because HGB-205 used a different product whose comparability to the Generation 1 product administered in HGB-204, and Generation 2 product used in the Phase 3 studies, could not be established. Inclusion of HGB-205 data in the labeling has not been decided, and still under review.

## 2. Additional Applicant Data

There was no discussion of additional data at the meeting.

## 3. Information Requests

- a. CMC IR #5 sent May 13, 2022. Responses received May 20, 2022 and are under review.
- b. As review continues, new information requests will be conveyed as warranted.

## 4. Discussion of Upcoming Advisory Committee Meeting

Bluebird asked if there would be a question-and-answer session after their LVV safety presentation at the AC meeting, who the LVV expert for the AC is, and what topics the expert will cover.

FDA confirmed that there would be a question-and-answer session after each AC presentation session and bluebird should reach out to Cristina Vert with their questions about the experts and AC agenda.

Bluebird noted that in the AC briefing document, both their current and proposed integration site analysis algorithms, were included. The proposed regulatory reporting has been implemented, but the new algorithm has not. Bluebird asked for FDA thoughts on the proposed algorithm and if this would be discussed at the AC.

FDA reiterated that the review is ongoing and cannot comment on the acceptability of the proposed algorithm at this time. Discussion topics for the AC are listed in the briefing document provided.

## 5. Postmarketing Requirements/Postmarketing Commitments

Review of pharmacovigilance plan, including applicant proposed postmarketing long term follow up study, is ongoing.

6. Major Labeling Issues

- a. No major labeling issues have been identified at this time.

7. Review Plans

- a. Review is ongoing.
- b. Label will be sent to applicant for negotiations by July 21, 2022.

8. Applicant Questions

There were no additional questions discussed.

9. Wrap-up and Action Items

Bluebird summarized:

IR review is ongoing and bluebird is open to informal telecons, as needed. The clinical team had no additional questions for the bone marrow pathologists. Study HGB-205 was omitted from the AC briefing document due to lack of comparability. Bluebird summarized the AC LVV presentation topics and bluebird should reach out to Cristina Vert for questions about the AC experts. There will be a question-and-answer section following each AC presentation session. FDA acknowledged the integration site algorithm implementation plan. The AC briefing document should be referred to for discussion topics. PVP plan including Registry study REG-501 protocol is currently under review.

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.