

Our STN: BLA 125717/0

**MID-CYCLE COMMUNICATION  
SUMMARY**

February 4, 2022

bluebird bio, Inc.  
Attention: Eleanor Yu, PharmD  
60 Binney Street  
Cambridge, MA 02142

Dear Dr. Yu:

Attached is a copy of the summary of your January 18, 2022 Mid-Cycle Communication Teleconference with CBER. This memorandum constitutes the official record of the Teleconference. If your understanding of the Teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to STN 125717/0 in your 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,

Tejashri Purohit-Sheth, MD  
Director  
Division of Clinical Evaluation  
and Pharmacology/Toxicology  
Office of Tissues and Advanced Therapies  
Center for Biologics Evaluation and Research

## Mid-Cycle Meeting Summary

**Application type and number:** BLA 125717/0  
**Product name:** betibeglogene autotemcel [ZYNTEGLO]  
**Proposed Indication:** Treatment of patients with  $\beta$ -thalassemia who require regular red blood cell (RBC) transfusions  
**Applicant:** bluebird bio, Inc.  
**Meeting date & time:** January 18, 2022 at 12 PM  
**Committee Chair:** Jakob Reiser, PhD  
**RPM:** Mona Badawy and Cara Pardon, MS

### FDA Attendees:

Meghna Alimchandani, MD, CBER/OBE  
Firoozeh Alvandi, MD, CBER/OBE/DE/PB  
Mona Badawy, CBER/OTAT/DRPM  
Kimberly Benton, PhD, CBER/OTAT  
Wilson W. Bryan, MD, CBER/OTAT  
Colleen Caldwell, MS, MPH, CBER/OTAT/DRPM  
Dennis Cato, CBER/OCBQ/DIS/BMB  
Esmeralda Alvarado Facundo, CBER/OCBQ/DBSQC  
Varsha Garnepudi, PhD, CBER/OCBQ/DBSQC  
Leila Hann, CBER/OTAT  
Jiang Hu, CBER/OBE/DB  
Lin Huo, PhD, CBER/OBE/DB  
Karl Kasamon, MD, CBER/OTAT/DCEPT  
Kristine Khuc, PharmD, CBER/OCBQ/DCM/APLB  
Anna Kwilas, PhD, CBER/OTAT/DCGT  
Carolyn Laurencot, PhD, CBER/OTAT/DCGT  
Wei Liang, PhD, CBER/OTAT  
Kavita Natrajan, MD, CBER/OTAT/DCEPT  
Adamma Mba-Jonas, MD, MPH CBER/OBE/DE/PB  
Leyish Minie, MSN, RN, CBER/OTAT/DRPM  
Cara Pardon, MS, CBER/OTAT/DRPM  
Steven Oh, PhD, CBER/OTAT/DCGT  
Most Nahid Parvin, CBER/OCBQ/DBSQC  
Raj Puri, MD, PhD, CBER/OTAT/DCGT  
Tejashri Purohit-Sheth, MD, CBER/OTAT/DCEPT  
Jakob Reiser, PhD, CBER/OTAT/DCGT  
Tal Salz, PhD, CBER/OTAT/DCGT  
Sandhya Sanduja, PhD, CBER/OTAT/DCEPT  
Kimberly Schultz, PhD, CBER/OTAT/DCGT  
Mercedes Serabian, MS, DABT, CBER/OTAT/DCEPT  
Ramani Sista, PhD, CBER/OTAT/DRPM  
Lisa Stockbridge, PhD, CBER/OCBQ/DCM/APLB  
Rachael Strong, PhD, CBER/OTAT  
Brian Stultz, MS, CBER/OTAT/DCGT

Melek Sunay, PhD, CBER/OTAT/DCEPT  
Edward Thompson, CBER/OTAT/DRPM  
Andrew Timmons, PhD, CBER/OTAT/DCGT  
Lori Tull, CBER/OTAT/DRPM  
Ramjay Vatsan, PhD, CBER/OTAT/DCGT  
Xiaofei Wang, PhD, CBER/OTAT/DCEPT  
Wei Wang, PhD, CBER/DMPQ  
Claire Wernly, CBER/OCBQ/DBSQC  
Julia Wright, MHA, RN, CBER/OTAT/DRPM

**Applicant Attendees:**

Richard Colvin, MD, PhD - Clinical Development, Chief Medical Officer  
Anne-Virginie Eggimann, MSc - Regulatory, Chief Regulatory Officer  
Marisa Gayron, MS - Biostatistics, Senior Director  
Divya Gupta, MSc - Regulatory Science, Manager  
Christopher Horvath, DVM, MSc - Preclinical Development, Senior Vice President  
Kelly Kral, MS - CMC Strategy and Operations, Senior Director  
Ankit Lodaya, MS - Pharmacovigilance, Associate Director  
Helena Madden, PhD - Regulatory Science - CMC, Senior Director  
Matthew Murphy - Regulatory Science - CMC, Associate Director  
Natasha Novikov, MD - Pharmacovigilance, Medical Director  
Aashita Parikh, MS - Regulatory Science, Director  
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

**Discussion Summary:**

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date.

Meeting Discussion

The review team has not identified any significant issues/major deficiencies at this time. No further discussion.

2. Information regarding major safety concerns.

Meeting Discussion

- a. FDA requested a beti-cel, rather than an eli-cel, manufacturing run to be performed at the upcoming Lonza-Houston inspection. The applicant asked for the reasoning behind this request. FDA explained that this request was due to the use of the (b) (4) in the (b) (4) step of the beti-cel process but not in the eli-cel process. There were deviations described in the PPQ report for beti-cel that are associated with the (b) (4). Additionally, the control strategy established for (b) (4) (CPP)

and (b) (4) (CPP) for the beti-cel process is more complex because it includes a (b) (4) set point for each of these CPPs while only a (b) (4) set point is used in the eli-cel process.

- b. FDA noted safety concerns regarding delayed platelet engraftment followed by prolonged thrombocytopenia of mild to moderate severity, which could potentially reflect deleterious impact of beti-cel on marrow function. These concerns arise from the observed dyserythropoietic changes with ringed sideroblasts and occasional atypical megakaryocytes reported from some beti-cel treated subjects' Month 12 and Month 24 bone marrow aspirates, in the setting of thrombocytopenia. In light of MDS/AML reported following similar sickle cell disease LVV product and cases of MDS with predominant clone in related LVV product for CCALD, this marrow pathology warrants further evaluation.

FDA reiterated prior requests for full bone marrow pathology reports. Although bone marrow aspirate data were provided as entries in excel spreadsheets, there were several blank fields, particularly for pathologists' assessment of findings and conclusions, limiting FDA's interpretation of these data entries. Reiterating the importance of thorough review of bone marrow findings with respect to product safety, FDA explained that it is crucial that the actual bone marrow aspirate reports from the reading pathologist be submitted for FDA review. The Applicant noted that the results were obtained from a contractor, but will do their due diligence to obtain reports from the third party laboratory and submit to FDA. Additionally, the Applicant proposed to have an independent pathologist read the bone marrow aspirate results and submit the pathologist's report to FDA for review. FDA agreed to this proposal, but emphasized that this would be in addition to, and not in lieu of submission of the original bone marrow aspirate marrow pathology reports.

3. Preliminary Review Committee thinking regarding risk management.

#### Meeting Discussion

- a. REG-501 study protocol and proposed PVP are under ongoing review.
- b. The applicant provided that REG-501 will be amended following withdrawal of beti-cel in the European market. FDA asked for a red-line version of the changes along with rationale/justification for the changes be submitted as soon as possible. The applicant stated this amended protocol would not be ready for 4-6 weeks. The agency asked that while this is being prepared, bluebird provide updated sample size and milestone dates, and the rationale for changes to sample size and milestone dates for review.

4. Any information requests sent, and responses not received.

Meeting Discussion

- a. Three pending requests:
    - 1) Clinical IR #8, sent January 6, 2022, is due January 20, 2022.
    - 2) Clinical IR #14, sent January 12, 2022, is due January 26, 2022.
    - 3) DBSQC IR #2 sent January 6, 2022, is due February 5, 2022.
  - b. FDA requested that the contracted independent pathologist reviewing the bone marrow biopsy specimens would also perform standard of care work up of the cases on the bone marrow samples to rule out MDS and other pathology, to include molecular cytogenetics, as warranted. The applicant communicated that an extension for this IR would likely be needed and would update the FDA as soon as possible with an expected submission date.
5. Any new information requests to be communicated.
    - a. As review continues, new information requests will be conveyed as warranted.

Meeting Discussion

No further discussion.

6. Proposed date(s) for the Late-Cycle meeting (LCM).
  - a. The LCM date will be provided at a later date.

Meeting Discussion

No further discussion.

7. Updates regarding plans for the AC meeting.

Meeting Discussion

The AC meeting will be rescheduled for late Spring/Early Summer. No separate CMC session is planned. FDA will have a retroviral vector expert present and bluebird will include a high-level manufacturing process summary.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.

### Meeting Discussion

Any updated milestone dates not provided in the Major Amendment letter, will be provided at a later date. No further discussion.