



Our STN: BLA 125755/0

**MID-CYCLE COMMUNICATION
SUMMARY**
April 7, 2022

bluebird bio, Inc.
Attention: Sarah Scott, PharmD
Senior Manager, Regulatory Science
60 Binney Street
Cambridge, MA 02142

Dear Dr. Scott:

Attached is a copy of the summary of your March 8, 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 BLA 125755/0 in your future submissions related to elivaldogene autotemcel.

If you have any questions, please contact Colleen Caldwell and Julia Wright at Colleen.Caldwell@fda.hhs.gov and Julia.Wright@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 Communication Summary

Application type and number: BLA 125755/0
Product name: elivaldogene autotemcel [SKYSONA]
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: bluebird bio, Inc.
Meeting date & time: March 8, 2022, 2:00pm - 3:00pm ET
Committee Chair: Anna Kwilas, PhD
RPMs: Julia Wright and Colleen Caldwell

FDA Attendees:

Lara Akinsanya, MS, CBER/OTAT/DRPM
Meghna Alimchandani, MD, CBER/OBE
Esmeralda Alvarado Facundo, PhD, CBER/OCBQ/DBSQC
Marie Anderson, PhD, CBER/OCBQ/DBSQC
Rachael Anatol, PhD, CBER/OTAT
Kimberly Benton, PhD, CBER/OTAT
Melanie Blank, MD, CBER/OTAT/DCEPT
Danielle Brooks, PhD, CBER/OTAT/DCEPT
Wilson Bryan, MD, CBER/OTAT
Colleen Caldwell, MS, MPH, CBER/OTAT/DRPM
Dennis Cato, CBER/OCBQ/DIS/BMB
Leah Crisafi, MD, CBER/OTAT/DCEPT
Shelby Elenburg, MD, CBER/OTAT/DCEPT
Alyssa Galaro, PhD, CBER/OTAT/DCEPT
Denise Gavin, PhD, CBER/OTAT/DCGT
Leila Hann, CBET/OTAT
Elizabeth Hart, MD, CBER/OTAT/DCEPT
Lin Huo, PhD, CBER/OBE
Adnan Jaigirdar, MD, FACS, CBER/OTAT/DCEPT
Beatrice Kallungal, MS, CBER/OTAT/DRPM
Anna Kwilas, PhD, CBER/OTAT/DCGT
Wei Liang, PhD, CBER/OTAT/DCEPT
Shuya (Joshua) Lu, PhD, CBER/OBE
Carrie Mampilly, CBER/OCBQ/DIS
Narayan Nair, CBER/OBE/DE
Tyree Newman, MDiv, CBER/OTAT/DRPM
Manette Niu, MD, CBER/OBE
Cara Pardon, MS, CBER/OTAT/DRPM
Tejashri Purohit-Sheth, MD, CBER/OTAT/DCEPT
Jakob Reiser, PhD, CBER/OTAT/DCGT
Kimberly Schultz, PhD, CBER/OTAT/DCGT
Brian Stultz, PhD, CBER/OTAT/DCGT

Ramani Sista, PhD, CBER/OTAT/DRPM
Lisa Stockbridge, PhD, CBER/OCBQ/DCM/APLB
Alisha Thomas, MD, MPH, CBER/OBE
Andrew Timmons, PhD, CBER/OTAT/DCGT
Lori Tull, CBER/OTAT/DRPM
Xiaofei Wang, PhD, CBER/OTAT/DCEPT
Allen Wensky, PhD, CBER/OTAT/DCEPT
Julia Wright, MHA, RN, CBER/OTAT/DRPM
Iwen Wu, PhD, CBER/OTAT/DCEPT

Applicant Attendees:

Melissa Bonner, PhD, Senior Vice President, Research
Richard Colvin, MD, Chief Medical Officer
Laura Demopoulos, MD, Vice President, Pharmacovigilance
Anne-Virginie Eggimann, MSc, Chief Regulatory Officer
Nicole Floro, MS, Senior Director, Pharmacovigilance
(b) (4), PharmD, Senior Consultant, Regulatory Science
Lin Pan, MS, Director, Biostatistics
Geoff Parsons, PhD, Senior Director, Research
Frederic Prince, PhD, Vice President, Program Lead eli-cel
Sarah Scott, PharmD, Senior Manager, Regulatory Science
Weiliang Shi, PhD, Vice President, Clinical Development Operations
Jakob Sieker, MD, Senior Medical Director, Clinical Research Development
Leslie Wilder, MS, Vice President, Regulatory Science – CMC

Mid-Cycle Comments/Discussion Summary:

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

Clinical:

The pivotal trial for this BLA is Study ALD-102. The primary efficacy endpoint is 24-month Major Functional Disability (MFD)-free survival. Success is defined as >50% of subjects achieving MFD-free survival at 24 months.

MFD-free survival is defined as being alive without any MFDs (loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, complete loss of voluntary movement), rescue cell administration/rescue HSCT, and without study withdrawal or loss of follow-up.

In addition to this primary benchmark comparison, you compared efficacy outcomes (MFD-free survival at 24 months and a time to analysis for MFD-free survival) in the ALD-102 population to a similar population in Study ALD-103. The SAP for the

comparisons between ALD-102 and ALD-103 did not pre-specify hierarchical statistics. We have identified the following issues.

- A. Although, FDA agreed to your benchmark analysis during your pre-BLA meeting in 2018, in the process of the BLA review, we now have concerns with using the benchmark of >50% MFD-free survival at 24 months as the primary endpoint. Arriving at a 50% clinical benchmark at 24 months was based on data from the ALD-101 subpopulation that received HSCT from a donor other than a matched sibling and had NFS scores of 0-1, Loes score of ≤ 9 , and gadolinium enhancement on brain MRI. However, this 50% benchmark relied heavily on the imputation strategy that considered repeat HSCT as a failure of MFD-free survival. As discussed below, we do not agree repeat HSCT should constitute failure. Without this imputation strategy, the benchmark would have been 89%.

Meeting Discussion:

Applicant discussed MFD-free survival using the updated data cut-off, and reiterated that they continue to find similar rates of MFD-free survival. Applicant asked if they understood FDA's concerns, and if the recently submitted adjustments reflect the current thinking on how MFD-free survival should be structured. FDA stated that they are still reviewing the submissions with the updated analyses and provided no further comments.

Applicant asked if FDA wants to change the benchmark. Applicant further noted that they are trying to demonstrate that eli-cel is comparable to Allo-SCT and asked if FDA agrees. FDA noted that the data are still under review and at this time the Agency is communicating one of the concerns with the primary efficacy endpoint review, and any further comments will be communicated after review.

- B. Comparability of external control groups is a major concern. This study was not a randomized controlled study, and thus there are known and unknown differences between the study groups that may have influenced results and impact interpretability. The two primary comparator populations used in your BLA submission are the ALD-102 eli-cel population and the strictly matched HSCT population without matched sibling donor (TPES NMSD) in Study ALD-103. The TPES NMSD populations in ALD-103 were older and had higher Loes scores at baseline compared to the ALD-102 population. Older age and higher Loes score are important baseline prognostic factors for disease progression. We are concerned that these factors could have biased the results in favor of eli-cel.

Meeting Discussion:

No further discussion

- C. In the comparator group in Study ALD-103, there were only 9 subjects without matched sibling donors who completed at least 24-months of follow-up. We are

concerned that there is insufficient data for an adequate comparison.

Meeting Discussion:

No further discussion

- D. We are concerned that 24 months is a short period for measuring efficacy outcomes in this debilitating disease, particularly because there were relatively few MFD events or deaths before 2 years across all similar study populations. Long-term data in the BLA submission are scant across populations. A longer observation time would be beneficial for a better understanding of the comparative efficacy between HSCT and eli-cel as well as the durability of eli-cel.

The recent report of a subject treated with eli-cel in Study ALD-104 who had loss of efficacy/ failure to achieve efficacy because of loss of eli-cel engraftment adds further concern regarding the durability of eli-cel relative to HSCT.

Meeting Discussion:

No further discussion

- E. We are not confident with the results of the statistical analyses which suggest eli-cel may be superior (and is at least non-inferior) to HSCT for efficacy outcomes.
- a. You provided propensity score analyses to overcome the baseline differences between ALD-102 and ALD-103 populations. We are concerned that propensity score analyses are insufficient to surmount the baseline differences between the treatment groups.
 - b. We do not agree with the imputation scheme, which favored eli-cel.
 - i. Repeat HSCT was imputed as equivalent to an MFD event or death. We do not agree with this imputation scheme because it is not conservative and HSCT is not equivalent to an MFD event or death.
 - ii. None of the cases of myelodysplastic syndrome (MDS) in the eli-cel populations (discussed below) were imputed as failure of MFD-free survival. Because MDS is associated with high mortality, not imputing MDS as a failure of MFD-free survival is not appropriate and biases the results in favor of eli-cel.

Meeting Discussion:

No further discussion

2. Information regarding major safety concerns.

- a. Our primary concern is MDS, a life-threatening disorder, that has occurred in 3 subjects. These cases have been determined to be possibly related to your product.

Meeting Discussion:

Applicant believes eli-cel still has a comparable benefit risk profile to Allo-SCT, and they discussed their thinking regarding how to integrate incidence of MDS cases into the benefit risk profile of eli-cel. Applicant noted that patients who would benefit the most from eli-cel would be determined on a case-by-case basis, and within the context of understanding the likely outcomes. In response to the applicant asking if this aligns with the FDA's thinking, the FDA stated the review is ongoing and had no further comments.

- b. We are concerned about the ISA showing increased relative frequency of integration and clonal expansion in genes known to be associated with malignancy. There are limited long-term clinical data which limits our understanding of the clinical significance of these insertions and appearance of predominant clones.

Meeting Discussion:

Applicant asked if FDA agrees with a more conservative 10% threshold, and FDA stated that the algorithm and threshold for reporting/ assessment of subjects cannot be discussed in this setting, as this affects other files in addition to this BLA. FDA requested an evidence-based rationale for FDA consideration of a different threshold.

- c. We are also concerned about the cases of Acute Myeloid Leukemia (AML) following treatment with a very similar LVV product in patients with sickle cell disease.

Meeting Discussion:

Applicant provided a root cause analysis summary of their understanding of AML cases observed in the sickle cell disease (SCD) program and potential malignancies in patients treated with eli-cel. Applicant stated leukemic blasts did not contain the LVV and were, therefore, not involved in the first patient's malignancy. Applicant stated the second patient's leukemic blasts also did contain integrated LLV, and their analysis determined the LLV was unlikely to have contributed to malignancy in this case and was a passenger mutation, not a driver.

Applicant agreed to submit the recently published article in the New England Journal of Medicine regarding AML in SCD to the BLA file. (Applicant confirmed post-meeting that the NEJM article was previously submitted to the BLA file under Amendment 7, SN0008).

FDA acknowledged different vectors can have different risk profiles, and the Agency is performing an analysis of the components of the vectors and what components may be potential risk factors. FDA is evaluating to determine any relationship or correlation between characteristics of the vectors/drug products and will reach out to the Applicant if any additional information is needed.

3. Preliminary Review Committee thinking regarding risk management.

MDS is a serious risk. The clinical team is considering whether a Risk Evaluation and Mitigation Strategy (REMS) is appropriate. The review team is also evaluating your proposed registry study, and are still evaluating what Post-Marketing Requirements/Commitments (PMR/PMC) may be required.

Meeting Discussion:

No further discussion

4. Any information requests sent and responses not received.

None at this time.

Meeting Discussion:

No further discussion

5. Any new information requests to be communicated.

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 between you and the Review Committee is currently scheduled for Tuesday, May 31, 2022, from 3:00pm to 4:30pm ET.
- b. We intend to send the LCM meeting materials to you approximately 11 days in advance of the LCM on May 20, 2022.

Meeting Discussion:

No further discussion

7. Updates regarding plans for the AC meeting.

The AC meeting will be held on June 9-10, 2022.

Meeting Discussion:

No further discussion

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

There are no changes at this time.

Meeting Discussion:

No further discussion