



Our STN: BL 125720/0

**LATE-CYCLE
MEETING MEMORANDUM**

July 1, 2020

BioMarin Pharmaceutical Inc.
Attention: Sabrina Gu
105 Digital Drive
Novato CA 94949

Dear Ms. Gu:

Attached is a copy of the memorandum summarizing your June 1, 2020 Late-Cycle teleconference with CBER. This memorandum constitutes the official record of the 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 Leyish Minie at (301) 796-5522.

Sincerely,

Raj Puri, PhD
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: June 1, 2020; 10:00 a.m.- 11:00a.m. EST
Application Number: BLA 125720/0
Product Name: valoctocogene roxaparvovec
Proposed Indications: For adults with severe hemophilia A (congenital factor VIII deficiency) (b) (4) without antibodies to adeno-associated virus serotype 5 detected by an FDA approved test.
Applicant Name: BioMarin Pharmaceutical Inc.

Meeting Chair: Andrew W. Harmon, PhD

Meeting Recorder: Leyish Minie, MSN, RN

FDA ATTENDEES

Emmanuel Adu-Gyamfi, PhD, CBER/OTAT/DCGT
Rachael Anatol, PhD, CBER/OTAT
Marie Anderson, CBER/OCBQ/DBSQC/LMIVTS
Kimberly Benton, PhD, CBER/OTAT
Lea Carrington, MD CDRH/OPEQ/OIDRH/DIHD
Denise, Cato, CBER/OCBQ/DIS/BMB
Graca Does, MD, MPH, CBER, OBE
Bradley Dworak, CBER/OCBQ/DMPQ/BI
Mona Elmacken, MD, CBER/OTAT/DCEPT/CHB
John Eltermann, CBER/OCBQ/DMPQ
Bindu George, MD, CBER/OTAT/DCEPT
Feorillo Galivo, MD, PhD, CBER/OTAT/DCEPT
Andrew Harmon, PhD, CBER/OTAT/DCGT
Colonious King, CBER/OCBQ/DIS/BMB
Simleen Kaur, CBER/OCBQ/DBSQC/LMIVTS
Arifa Khan, CBER/OVRR/DVP/LR
Kristine Khuc, PhD, CBER/OCBQ/DCM/APLB
Donald Lech, CBER/OCBQ/DMPQ/BI
Wei Liang, PhD, CBER/OTAT/DCEPT
Yuqun (Abigail) Luo, PhD, CBER/OBE
Leyish Minie, MSN, RN, CBER/OTAT/ DRPM
Nair Narayan, MD, CBER/OBE
Steven Oh, PhD, CBER/OTAT/DCGT
Mikhail Ovanosov, PhD, CBER/OTAT/DPPT
Lori Peters, CBER/OCBQ/DMPQ/BI
Raj Puri, MD, PhD, CBER/OTAT/DCGT
Tejashri Purohit-Sheth, MD, CBER/OTAT/DCEPT
Renee Rees, PhD, CBER/OBE
Andrey Sarafanov, PhD, CBER/OTAT/DPPT
John Scott, PhD, CBER/OBE/DB

Ramani Sista, PhD, CBER/OTAT/DRPM
Zenobia Taraporewala, PhD, CBER/OTAT/DCGT
Natasha Thorne, PhD, CDRH
Lori Tull Lori Tull, CBER/OTAT/DRPM
Xiaofei Wang, PhD, CBER/OTAT/DCEPT
Kerry Welsh, MD, CBER/OBE
Allen Wensky, PhD, CBER/OTAT/DCEPT
Iwen Wu, PhD, CBER/OTAT/DCEPT

APPLICANT ATTENDEES

Robert Baffi, PhD, President, Global Manufacturing and Technical Operations
Lon Cardon, PhD, Senior Vice President, CSO, Research and Development
Sianna Castillo, PhD, Director, Regulatory Affairs
Mairead Duke, PhD, Executive Director, Regulatory Affairs CMC
Henry Fuchs, MD, President, Worldwide Research & Development
Brad Glasscock, PharmD, Group Vice President, Head of Global Regulatory Affairs
Sabrina Gu, MS, Sr. Director, Regulatory Affairs
Joshua Henshaw, PhD, Sr. Director, Clinical Pharmacology
Chito Hernandez, PhD, Group Vice President, BioMetrics, Global Clinical Sciences
Kala Jayaram, MD, Executive Medical Director, Pharmacovigilance
Ben Kim, MD, MPhil, Executive Medical Director, Clinical Science
Elizabeth Marsie-Hazen, PhD, Senior Director, Product Quality Leader, Quality
Jennifer Mercer, PhD, Vice President, Regulatory Affairs CMC
Elizabeth Moyle, Executive Director, Regulatory Affairs
Geoff Nichol, MB ChB, MBA, Senior Vice President, CMO, Head of Global Clinical Development
James Nickas, PharmD, Vice President, Pharmacovigilance
Chuck O'Neill, PhD, DABT, Vice President, Pharmacological Sciences
Nina Orike, PhD, PMP, Sr. Director, Global Project Management
Hayley Pemble, PhD, Associate Director, Regulatory Affairs
Parvin Perrino, MS, Sr. Director, Regulatory Global Labeling
Tammy Rose, Executive Director, Regulatory Affairs
Victoria Sluzky, PhD, Senior Vice President, Quality and Product Development
Gordon Sun, PhD, Vice President, Biostatistics
Harmit Vora, PhD, Director, Process Sciences
Wing Yen Wong, MD, Vice President, Clinical Sciences
Xinqun Yang, PhD, Executive Director, Biostatistics, Global Clinical Sciences
Stephen Zoog, PhD, Vice President, Translational Sciences

External Attendee:

(b) (4)

BACKGROUND

STN BL 125720/0 was submitted on December 23, 2019, for valoctocogene roxaparvovec.

Proposed indication: For adults with severe hemophilia A (congenital factor VIII deficiency) (b) (4) without antibodies to adeno-associated virus serotype 5 detected by an FDA approved test.

PDUFA goal date: August 21, 2020

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on May 22, 2020.

Discussion

1. Discussion of Substantive Review Issues

Chemistry, Manufacturing, and Controls:

1. BioMarin's proposal to use a (b) (4) method (as the dose-determining assay) for the assignment of vector strength (b) (4) of the Drug Product (DP), instead of the (b) (4) methods used for IND studies, respectively: The proposal is under review and no additional information requests are anticipated.
2. BioMarin's proposal to change testing for (b) (4) release requirement to in-process characterization (monitoring) only: The proposal and the additional information submitted under Amendment 25 (eCTD Sequence 27, received 3 April) are under review, and no additional information requests are anticipated.
3. The proposed shelf-life for the (b) (4) DP: Additional data provided to support shelf life duration with 95% confidence, under Amendment 33 (eCTD Sequence 34, received 17 April) is currently under review, however the data does not support the proposed (b) (4) -month expiry date for DP and (b) (4) -month expiry date for (b) (4). Please note that we are not currently asking for additional supporting stability data, and a decision on the stability period will be made based on the data we have received.
4. Lot release specifications for the (b) (4) DP remain under review. Upon completion of the review, the review team will communicate with BioMarin to reach final agreement on the specifications for commercial lot release.

5. Residual DNA impurities in the product: The information from additional characterization studies discussed during a telephone conference on 6 March and submitted under Amendment 20 (eCTD Sequence 22, received 23 March) that notes the level of DNA impurities in the (b) (4) lots is currently under review. Notably, the levels (b) (4) of (b) (4) , are far in excess of the (b) (4) , which is the only measure of residual DNA proposed in the (b) (4) release testing plan. Considering that the accuracy of your proposed dose determining assay (b) (4) is reliant on control of (b) (4) , and the unknown risk of high amounts of these residual DNA (b) (4) revisions to the release testing plan to include testing for (b) (4) should be anticipated. Related information requests should be expected with the completion of the review.

Meeting Discussion:

There was no additional discussion of items 1 and 2. Regarding item 3, BioMarin acknowledged receipt of an information request (IR) sent by FDA on Friday 29 May 2020 detailing FDA's rationale for denying the proposed (b) (4) DP expiry dating. BioMarin stated that a response to this IR will be submitted on Friday 5 June 2020. Regarding items 4 and 5 BioMarin inquired about the possibility of scheduling a teleconference (Tcon) with the FDA CMC team. FDA did not agree to an additional Tcon but advised BioMarin to contact the Regulatory Project Manager (RPM) with specific questions or concerns and that a Tcon could be scheduled if necessary.

Clinical:

6. Efficacy

- a. We have observed substantial differences in the efficacy outcomes between Study 301 and Study 201 that limit our ability to extrapolate the durability results observed in Study 201 to Study 301.
- b. We have observed substantial differences in the use of systemic steroids between Study 301 and Study 201 that further limit our ability to
 - i. Evaluate the durability of the responses observed in Study 301 and
 - ii. Understand and isolate the contribution of the prolonged and variable systemic corticosteroid use to the treatment effect and efficacy outcomes. Thus, the efficacy results may be confounded by the use of systemic steroids.

- c. The substantial inter- and intra-patient variability in the FVIII activity level time-course and limited sample size pose a challenge in predicting future activity levels and relating observed levels to bleeding rates.

Meeting Discussion:

FDA expressed a concern regarding the differences between Studies 201 and 301 in terms of the response and the initial durability of response in Study 301 with respect to factor VIII levels. FDA also noted the substantial difference in systemic steroid use between the two trials. As a result, FDA is uncertain as to the durability of the FVIII response and associated risk of bleeding, as well as the contribution of prolonged systemic steroid use towards the FVIII response reported in Study 301. In addition, with respect to the time course for the observed factor VIII activity, FDA noted that there is substantial inter and intra patient activity level variability. Given the limited sample size, it is very difficult to understand future factor VIII activity levels as well as the levels that may trigger bleeding events.

7. Safety

- a. We are concerned regarding the limited safety follow-up period and limited data to assess the risks of vector integration, clonal expansion of cells with integration, and potential for insertional mutagenesis. If your product receives marketing approval, we may require post-marketing study(ies) and product labeling that address these safety concerns. For example, considerations include, but are not necessarily limited to, the following:
 - i. A post-marketing study to obtain follow-up safety data for up to 15 years for all subjects treated with the investigational product.
 - ii. A post-marketing study to obtain additional data to assess the risk of vector integration.
 - iii. Warnings, including a possible boxed warning, in the package insert to inform healthcare providers and patients of the anticipated risks.

Meeting Discussion:

As the safety follow-up period is limited, there are limited data to assess the risk of vector integration and potential long-term risks of malignancy from expansion of the cell following integration and the possibility of mutagenesis. If and when a marketing approval is planned for the investigational product, FDA may require postmarketing studies and modifications to the proposed label to note the safety concerns. Considerations include a Long Term Follow up Study up to 15 years, need to obtain additional data to assess the risk of integration, and from a labeling perspective, potential for a Boxed Warning.

2. Additional Applicant Data
BioMarin shared a high level four years data of 201 study.
3. Discussion of Upcoming Advisory Committee Meeting
No Advisory Committee Meeting issues were discussed during the Late-Cycle Meeting.
4. Risk Management Actions (e.g., REMS)
There is no anticipation of a REMS at this time.
5. Postmarketing Requirements/Postmarketing Commitments

Chemistry, Manufacturing, and Controls:

Requirements for post marketing commitments for CMC topics will be discussed with the applicant via electronic communication and agreement on the scope and timing of these commitments is expected to be achieved by 21 July 2020.

Epidemiology:

The Pharmacovigilance Plan is under review at this time.

6. Major Labeling Issues
No Labeling issues were discussed during the Late-Cycle Meeting.
7. Review Plans
The review of the application is currently ongoing.
8. Applicant Questions
9. Wrap-up
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.