



Our STN: BL 125720/0

COMPLETE RESPONSE

August 18, 2020

BioMarin Pharmaceutical Inc.
Attention: Sabrina Gu
Senior Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Gu:

Please refer to your Biologics License Application (BLA) submitted and received on December 23, 2019, for valoctocogene roxaparvovec manufactured at your Novato, California location and submitted under section 351(a) of the Public Health Service Act.

We have completed our review of all the submissions you have made relating to this BLA with the exception of the information in the amendment submitted and received on August 6, 2020, as noted below. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

Clinical

1. Your BLA does not provide sufficient evidence of the effectiveness of your product. You provided the results from two studies, Studies 270-301 (interim analysis) and 270-201, to support the effectiveness of valoctocogene roxaparvovec. Study 270-301, the primary study intended to support a marketing application, is an ongoing, single-arm, open-label study in 130 subjects with hemophilia A (HA) with residual FVIII activity levels ≤ 1 IU/dL; all subjects in Study 270-301 receive a dose of 6E13 vg/kg. The interim analysis of Study 301 consists of efficacy data from 22 treated subjects and safety data from 32 subjects. Study 270-201 was an open-label, dose-escalation study in 15 subjects; 7 subjects received the dose under consideration, 6E13 vg/kg, and were followed for 3 years. We have the following concerns regarding the data in your BLA.
 - a. You have not provided sufficient evidence that your product has a durable effect. In your BLA, the majority of subjects in Study 270-301 have been followed for less than 12 months; therefore, Study 270-201 was expected to provide evidence of the long-term durability of the effect of your product. However, there are clinically important differences between the results of these two studies; these differences limit our ability to rely on

Study 270-201 to support durability of effect. In Study 270-301, we note significant inter- and intra-subject variability in factor levels over time, with substantial declines in FVIII levels in some subjects, with faster rates of decline than are seen in Study 270-201. The peak FVIII activity levels in Study 270-301 were much lower than the peak FVIII levels observed in Study 270-201. Four Study 270-301 subjects ($4/22 = 18\%$) had evident decline over time. At least three subjects ($3/22 = 14\%$) had activity levels of zero by Year 1. Additionally, 86% of subjects in Study 270-201, compared to 40% of subjects in Study 270-301, achieved the pre-specified responder status. It is unclear whether these clinical differences are due to changes that you made in the manufacturing process, differences in corticosteroid use between the two studies, or other factors. However, because the clinical activity of the product is substantially different in the two studies, the results of Study 270-201 are not a reliable indicator of the clinical activity of the Study 270-301 product, which you propose for commercial use.

Thus, Study 270-201 does not provide evidence of the durability of the effect of your proposed commercial product. In addition, Study 270-301 does not include long-term follow-up of a sufficient number of patients to assess the durability of the clinical activity of your product. In the absence of substantial evidence of a durable effect, we are not able to adequately determine whether the benefits justify the risks of your product in Hemophilia A. To provide such evidence, please complete Study 270-301 and submit 2-year follow-up safety and efficacy data on all Study 270-301 subjects.

- b. There are differences between the two studies with respect to administration of corticosteroids to treat elevations of transaminases. A greater proportion of subjects received corticosteroid treatment, and for longer duration, for the treatment of transaminase elevations in Study 270-301 compared to Study 270-201. Additionally, treatment doses of corticosteroids were initiated earlier in Study 270-201 as compared to Study 270-301. It is unclear if these differences in corticosteroid use led to the differences in the observed efficacy between the two studies. However, corticosteroids are expected to influence FVIII levels, and thus confound the treatment effect of your product, making the study results for Study 301 difficult to interpret. In the absence of additional evidence to define the treatment effect, and control for the confounding due to steroid use, we are not able to adequately determine whether the benefits justify the risks of your product in Hemophilia A.

Please address the potential confounding effects of corticosteroid use on treatment effect.

- c. The primary efficacy analysis for Study 270-301 was based on a candidate surrogate endpoint of responder status defined as having median FVIII activity level (b) (4) IU/dL during Weeks 23-26. Use of this endpoint as a surrogate in support of accelerated approval is contingent upon demonstrating that this threshold for FVIII activity level is reasonably likely to predict a clinically meaningful effect on annualized bleeding rate (ABR) in patients with severe hemophilia.

However, Study 301 IA results demonstrate substantial variability in FVIII activity over time, with substantial decline in FVIII activity level in some subjects. The substantial decline in FVIII activity over time in some subjects, including some responders, indicates that FVIII activity levels during Weeks 23-26 may not adequately summarize subsequent FVIII activity levels. In addition, Study 301 IA data do not demonstrate that FVIII activity responder status during Weeks 23-26 predicts benefit for ABR. Furthermore, the limited efficacy data available from Study 270-301 suggest that ABR may be a more suitable endpoint to assess the treatment effect of your product. Therefore, we recommend that you revise the Study 270-301 protocol and statistical analysis plan to specify ABR as the primary endpoint, with the primary efficacy assessment based on results through two years following product administration for all subjects.

2. Data from Study 270-301 suggest that some subjects may have an increased risk of bleeding after receiving your product. However, the data are limited by several factors, including the retrospective nature of the baseline bleeding rates, the small sample size, and the limited duration of follow-up. In order to support a reliable assessment of the risks to patients with Hemophilia A, Study 270-301 must provide sufficient evidence to reliably characterize the risk that your product may be associated with an increased risk of bleeding. Therefore, as noted above, we recommend that you complete Study 270-301, including 2-year follow-up on ABR on all Study 270-301 subjects.

Chemistry, Manufacturing, and Controls/Facility

3. Due to the inadequacy of the data submitted to support approval, the agency did not conduct a pre-license inspection of your manufacturing facility. This inspection will need to be performed after the agency receives a complete response with adequate data to address the deficiencies identified in this letter (21 CFR 601.3(a)(2)).
4. Your application did not contain sufficient information to assess the qualification of the (b) (4) used for sterilization of the materials that contact the final sterilized product. Please provide the following information:

- a. A summary of results of the (b) (4), including a diagram and identification of the (b) (4).
- b. Locations of (b) (4) placements in the (b) (4) and rationale for selection of monitoring locations.
- c. Name, lot number, labeled population, and expiration date for the (b) (4) used in the studies.
- d. The summarized data collected during (b) (4) tests, and your specifications regarding temperature differences allowed between temperature (b) (4).
- e. If applicable, a summary along with the results of the validation performed for a minimum (b) (4) configuration.

Labeling

5. We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling.

Within one year after the date of this letter, you are required to resubmit or withdraw the application (21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval.

Please submit your meeting request as described in the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf>, and CBER's SOPP 8101.1 *Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants* at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>.

We acknowledge receipt of your amendment dated August 6, 2020. Please be aware that we have stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response. You may cross reference applicable sections of the amendment dated August 6, 2020, in your complete response to this letter and we will review those sections as a part of your complete response.

In addition to the deficiencies that were the basis for not granting approval, we have identified the following deficiencies:

Clinical

6. In Study 270-201, liver biopsies from two subjects were noted to have (b) (4) of vector genome, based on a (b) (4) based assay. These findings raise concerns for vector integration as the (b) (4) assay on liver biopsies was not designed to differentiate (b) (4) forms of vector genome. The risk of such integration and any malignancy could be extremely important to patients with Hemophilia A who might consider using your product. Therefore, we recommend that you consider additional evaluations to assess the risks of vector integration and insertional mutagenesis and monitor study subjects for the risk of malignancies in the ongoing clinical trials for a period of at least 15 years.
7. Vector DNA shedding was observed in the seminal fluid of study subjects, raising concerns regarding risk of germline transmission. The Study 270-301 follow-up period to date is insufficient to adequately assess the duration of continued shedding in the seminal fluid. Therefore, please submit additional data to characterize the duration of vector DNA shedding in the seminal fluid. In addition, you may need clinical data from the ongoing studies of your product to address the potential for germline transmission.
8. Patients treated with your product who express the transgenic FVIII product may require administration of recombinant products for treatment of a bleeding episode and assessment of FVIII levels to inform management of subsequent doses of recombinant FVIII products. Determining FVIII levels is challenging because recombinant products are associated with higher chromogenic substrate (CS) assay readings, as compared to one-stage (OS) assay-based readings of FVIII levels if the same sample were to be assayed using both assay methods. For patients who have transgenic expression of FVIII activity levels, the CS assay readings were numerically lower than with the OS assay. Therefore, the management of dosing of recombinant products to achieve specific target levels of FVIII becomes challenging for the treating physician. Please collect and provide data to be able to provide advice to the prescriber in a future label for your product regarding dosing and management of bleeding or peri-operative bleeding.
9. In Study 270-301, FVIII activity levels declined following use of concomitant medications such as isotretinoin and dextroamphetamine/amphetamine. Please provide a plan to collect data to assess the impact of drugs that may affect FVIII activity levels or result in hepatic cellular injury.

Chemistry, Manufacturing, and Controls

10. Regarding (b) (4) in the valoctocogene roxaparvovec (b) (4), we have reviewed the data submitted in Module 3.2.S.3.2 as well as the risk analysis you provided via Amendment 20 (eCTD sequence 22, received 23 March 2020) addressing concerns about the expression of antibiotic resistance genes and transposase, the potential for recombination events, and DNA integration. However, we do not agree that the information you provided is adequate to justify relying on a single release test (b) (4) to control and monitor (b) (4) from the (b) (4).

- a. You must include release testing for representative sequence(s) from (b) (4)
- b. Testing for (b) (4) from the (b) (4) must include sequence(s) representative of (b) (4)
Your data suggests that (b) (4) may be as high as (b) (4) than levels of (b) (4) in a commercial dose. We note your analysis is also in agreement with this conclusion, stating (b) (4)
- c. You should set appropriate acceptance criteria for these tests, and your BLA should be updated to reflect this release specification (test and acceptance criterion) as well as relevant descriptions of the assay and validation data. Please note that this testing requirement is to assure compliance with 21 CFR 610.13, "Products shall be free of extraneous material except that which is unavoidable in the manufacturing process described in the approved biologics license application." Acceptability of this specification will be reviewed in a future BLA submission.

11. Regarding the validation of the in-process material hold times described in Module 3.2.S.2.4 (Table 3.2.S.2.4.1.1), we are currently unable to determine how representative the (b) (4) validation study is to the (b) (4) manufacturing process. Please submit the full validation report (PVR-24008) and data to support the hold times. Also note the following related concerns:

- a. The BLA does not contain (b) (4) data supporting a hold of (b) (4) lots generated from the PPQ campaign use (b) (4) storage of (b) (4). Review of PVR-24008 is necessary to determine if the (b) (4) study supports this hold.
- b. Module 3.2.S.2.4. describes (b) (4) holds that occur for the (b) (4) in-process material. This material is described as being held (b) (4). These holds are not adequately

described in the results of the PPQ campaign (Module 3.2.S.2.5) or the description of the (b) (4) manufacturing process (3.2.S.2.2).

12. Please describe and clarify the storage locations for the (b) (4) held frozen ($\leq -60^{\circ}\text{C}$) and at $2-8^{\circ}\text{C}$. Please include qualification summary reports demonstrating adequacy of the storage environment and conditions for these locations.

Statistical

Limitations in the design and conduct of Study 270-301 pose challenges to estimate precisely the magnitude of treatment effect compared with routine prophylaxis. Precise estimate of treatment effects is important to inform FDA's benefit-risk assessment. Please consider the following statistical aspects as you complete Study 270-301.

13. Joint analysis of annualized bleeding rate (ABR) and exogenous FVIII use. Because ABR and exogenous FVIII use are not independent, joint analysis, in addition to univariate analysis, should be performed to characterize individual-level treatment effect.
 - a. You use "Week (b) (4) and Beyond" as the period for evaluating treatment efficacy. This choice related to the plan for subjects to receive FVIII prophylaxis as needed for the first four weeks following valoctocogene roxaparvovec infusion. However, Subject (b) (6) received exogenous FVIII replacement for 62 days during the first 76 days after valoctocogene roxaparvovec infusion. Several more subjects received prophylaxis FVIII on Day 33, the boundary of the efficacy analysis period. We recommend that you use an individualized efficacy analysis period, based on each subject's prophylactic treatment with exogenous FVIII. This period may vary between subjects and should start after the effect from the last prophylaxis FVIII after valoctocogene roxaparvovec infusion is thought to have ended.
 - b. Some subjects received exogenous FVIII infusions during the baseline period at a frequency lower than expected of adequate routine prophylaxis. For example, eight subjects had baseline annualized infusion rate (AIR) of less than 100 days/year (range: 49 to 97). This raises a concern whether all these subjects satisfied the eligibility criterion of "*Must have been on prophylactic FVIII replacement therapy for at least 12 months prior to study entry.*" In addition, if a subject had little or no bleeding despite receiving FVIII replacement less frequently than expected of typical routine prophylaxis, it is difficult to conclude with confidence that a good bleeding outcome post-treatment with valoctocogene roxaparvovec was in fact due to valoctocogene roxaparvovec treatment. Please include subject-level information of FVIII use and ABR for both the baseline period and efficacy evaluation period.

Graphical aids such as swimmer plots can be useful for such within-subject analyses.

- c. One reason provided for exogenous FVIII product use was “One-time Factor VIII prophylaxis” (Study 301, adcm.xpt, variable CMSCAT). In particular, Subject (b) (6) had 17 instances of “One-time Factor VIII prophylaxis,” while another five subjects each had one instance. Please provide more specific descriptions of “One-time Factor VIII prophylaxis” for these 22 instances and how they should affect the efficacy assessment during the efficacy evaluation period (EEP). For example, Subject (b) (6) all-bleed ABR went from 11.4 at baseline to 12.7 over an EEP of 12.3 months (i.e., after Day 33), with a 70% reduction in AIR post-treatment (from 143 at baseline to 43 post-treatment). It appears that this subject’s reduction in AIR was due to switching from routine prophylaxis at baseline to a post-treatment on-demand use pattern of FVIII infusions, rather than due to a beneficial effect of valoctocogene roxaparvovec for this subject. Please confirm our interpretation or provide an alternative interpretation.
14. Multiple and inconsistent protocol amendments have complicated the interpretability of the results submitted in the BLA. For example, at the time of BLA filing on December 23, 2019, Study 270-301’s most recent protocol was amendment 4 (dated November 9, 2018), where “*An interim analysis is planned after 20 treated HIV-negative subjects have completed the Week 26 visit.*” Three months after the BLA was filed, protocol amendment 6 was submitted to IND 17659, where “*Instead of one interim analysis as originally planned, two interim analyses were planned after the first approximately 16 and 20 HIV-negative have completed the Week 26 visit (or have discontinued study participation prior to Week 26), respectively.*” Protocol amendment 5 was not submitted. Pre-specification of analyses is a bedrock principle of the statistical interpretation of clinical trials; inconsistencies and frequent changes jeopardize the interpretability of results. Please submit any future protocol amendments in a timely fashion, with summaries of changes and explanations for the changes, and include a full timeline of protocol amendments and their purpose in your complete response to this letter.
15. FVIII activity level time course.
 - a. Reporting average FVIII activity level across individuals with available data at given time points may not accurately reflect the true average. For example, Subject (b) (6) had zero activity levels except for three measurements during his 406-day follow-up. His last three measurements were separated by 90 days and 78 days. Subject (b) (6) last measurement of an activity level of 0 was 50 days before the end of his follow-up period. These intervals are much wider than the schedule in the protocol, i.e., biweekly from Week 36 to Week 52 and every four weeks for

Year 2. Please do not exclude such subjects from calculations but instead use an appropriate imputation method. For these particular subjects, imputing a value of zero for the missing FVIII activity levels would appear to be appropriate.

- b. You have provided individual-level FVIII activity level time course graphs for all subjects. As an additional descriptive analysis, we recommend that you categorize individual time courses into meaningful categories, e.g., relative stable after reaching x activity level or after a given time point, or rapid decline during y period, or continued increase through Day z, etc.

Clinical Pharmacology

- 16. High variability was observed in the cellular immunogenicity assays. You may consider using (b) (4) to improve the performance of cellular immune response assays. In addition, Study 270-201 cellular immunogenicity assessments indicate intermittent cellular responses in several subjects in response to stimulation with hFVIII-SQ (b) (4) in the (b) (4) ELISPOT assay. However, Study 270-301 cellular immunogenicity assessments do not include (b) (4) ELISPOT assay. Please consider adding the (b) (4) ELISPOT assay to future cellular immunogenicity monitoring for Study 270-301.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Leyish Minie, at (301) 796-5522.

Sincerely,

Wilson W. Bryan, MD
Director
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research