

CBER CMC BLA Resubmission Review Memorandum

BLA STN 125720

**valoctocogene roxaparvovec-rvox
ROCTAVIAN**

Reviewers

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1. BLA#: STN 125720

2. APPLICANT NAME AND LICENSE NUMBER

BioMarin Pharmaceutical Inc.

3. PRODUCT NAME/PRODUCT TYPE

Non-Proprietary/USAN: valoctocogene roxaparvovec-rvox

Proprietary Name: ROCTAVIAN

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

Pharmacological category: Adeno-associated virus vector-based gene therapy

Dosage form: Suspension for injection

Strength: 2.0×10^{13} vector genomes (vg) / mL

Route of administration: Intravenous

Indication: For treatment of adults with severe Hemophilia A (congenital factor VIII deficiency) (b) (4) without

antibodies to adeno-associated virus serotype 5 (AAV5) detected by an FDA-approved test.

5. MAJOR MILESTONES

Received: December 23, 2019

Filed: February 21, 2020

Mid-cycle Communication: April 20, 2020

Late-cycle Meeting: June 1, 2020

Complete Response Letter Issued: August 18, 2020

Original Submission PDUFA action due: August 21, 2020

Type A Meeting: October 29, 2022

Type 2 Resubmission Received: September 29, 2022

Major Amendment Filed: February 15, 2023

Type 2 Resubmission Original PDUFA action date: March 31, 2023

Type 2 Resubmission Major Amendment PDUFA action date: June 30, 2023

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Emmanuel Adu-Gyamfi PhD, OTP/OGT/DGT1/GTB1	As indicated in the review
Andrew Harmon PhD, OTP/OGT/DGT1/GTB1	As indicated in the review
Y Nguyen PhD, OTP/OGT/DGT1/GTB2	As indicated in the review
Mikhail Ovanesov, PhD, OTP/OPPT/DH/HB2	As indicated in the review

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)

Natasha Thorne PhD, Hematology Branch, Division of Immunology and Hematology Devices, Office of In Vitro Diagnostics and Radiological Health, Office of Product Evaluation and Quality, CDRH	AAV5 ImmunoDetectCDx, AAV5 Total Antibody (TAb) Assay	Yes
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8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
09/29/22	125720/0.69	Type 2 BLA Resubmission
10/19/22	125720/0.70	Response to DMPQ IR sent on 10/11/22
11/02/22	125720/0.71	Response to DMPQ IR sent on 10/26/22
12/20/22	125720/0.76	Response to PLI Inspection Observations
01/09/23	125720/0.77	Resubmission of proprietary name and suffix request
01/31/23	125720/0.80	Response to DGT IR sent on 01/17/23
02/07/23	125720/0.85	Response to DGT IR sent on 02/01/23
02/17/23	125720/0.93	Response to DBSQC IR sent on 02/10/23
02/17/23	125720/0.94	Response to DBSQC IR sent on 02/03/23
03/03/23	125720/0.97	Response to DBSQC IR (LRP Negotiation) sent on 02/27/23
03/06/23	125720/0.98	Response to DGT IR (Vial/Carton Label Negotiations) sent on 02/27/23
03/15/23	125720/0.99	Response to DBSQC IR (LRP Negotiation) sent on 03/14/23
04/14/23	125720/0.100	Submission of proposal to increase DP expiry to 36 months
04/24/23	125720/0.101	Response to DMPQ IR sent on 04/20/23
06/05/23	125720/0.107	Response to DGT IR sent on 05/30/23

9. Referenced REGULATORY SUBMISSIONS

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
DMF (b) (4)	(b) (4)	[REDACTED]	Yes	Review deferred to DMPQ
DMF [REDACTED]	(b) (4)	[REDACTED]	Yes	Review deferred to DMPQ
#PMA P190033	ARUP Laborato ries	AAV5 ImmunoDetect CDx, AAV5 Total Antibody (TAb) Assay	Yes	Reviewed by CDRH
DMF BB-MF [REDACTED]	(b) (4)	[REDACTED]	Yes	Review deferred to DMPQ
DMF STN [REDACTED]	(b) (4)	[REDACTED]	Yes	Review deferred to DMPQ
DMF BB-MF [REDACTED]	(b) (4)	[REDACTED]	Yes	Review deferred to DMPQ
DMF BB-MF [REDACTED]	(b) (4)	[REDACTED]	Yes	Review deferred to DMPQ

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

At the time of the Administrative Due Date (ADD) for the original BLA submission (08/21/20) the CMC review team had not identified major concerns that would prevent making an approval decision. However, a pre-license manufacturing facility inspection was unable to be conducted due to travel restrictions associated with the COVID-19 pandemic global health emergency and due to the decision that a complete response (CR) letter would be issued for inadequate clinical data. Following the CR decision, the review team instituted an information request (IR) cutoff on June 5, 2020, after which the CMC review team ceased sending IRs to the Applicant. At the time of the IR cutoff there were several CMC review issues which were not fully resolved, including agreement on release specifications and additional manufacturing review which would have been assessed during the pre-license facility inspection. A CR letter was issued to the Applicant on 08/18/20 requesting 2 years of subject follow-up data. The CR letter also included additional advice and informational comments from the DGT CMC discipline.

In preparation for BLA resubmission a Type A meeting was held on 10/5/20 and on 09/29/22 the Applicant resubmitted their BLA, which was accepted as a Class II resubmission with a 6-month review clock and an ADD of 03/31/23. The pre-license inspection of the BioMarin Novato manufacturing facility was held December 5-9, 2022. Two resolvable inspection observations were issued by DMPQ inspectors and an acceptable response to these observations was received from the Applicant on 12/20/22.

On 02/15/23, prior to the resubmission ADD, an amendment was received containing clinical data with 3 years of subject follow-up. This amendment was classified as a Major Amendment on 03/6/23, which resulted in a new ADD of 6/30/23.


Based on our review of the collective information submitted by the Applicant in the BLA resubmission and subsequent information requests reviewed throughout the review period, the CMC review team concludes that the manufacturing and controls for valoctocogene roxaparvovec-rvox (BMN270; ROCTAVIAN) are capable of yielding the drug product with consistent quality attributes deemed acceptable for commercial manufacturing under the BLA.

Description of the product:

Valoctocogene roxaparvovec-rvox is a suspension of an adeno associated virus (AAV) vector-based gene therapy for intravenous infusion. The active ingredient is a recombinant AAV vector, where the DNA vector genome is enclosed in a capsid that consists of (b) (4) serotype 5 AAV capsid proteins. The vector DNA lacks all AAV genes. The vector DNA contains a transgene encoding a (b) (4) B domain-deleted (BDD) human factor VIII (hFVIII) protein, under the control of a hybrid human liver-specific promoter (HLP).

Manufacturing and quality

The drug substance (DS) is manufactured by (b) (4)



The DP may be processed from the (b) (4)



After sterile filtration, DP is filled using a fully-automated filling line. Post-filling, unlabeled vials are frozen, placed in appropriately labeled secondary containment, and shipped to a contract manufacturing organization (CMO) for storage. Vials undergo primary labeling (under frozen conditions) and each vial is placed in a secondary packaging carton at the same CMO based on inventory management and market demand. Appropriate controls to maintain chain of custody, chain of identity, and vial reconciliation are in place to protect from mix-ups of unlabeled vials and labeling of previously frozen vials has been validated. Final identity testing of each lot in its final labeled container closure configuration is confirmed by identity testing prior to the formal release of the lot. Alternatively, DP vials may be labeled at (b) (4) conditions immediately following filling, however, this will not be the primary method of labeling at the time of BLA approval.

The DP has a nominal concentration of 2.0×10^{13} vector genomes (vg)/mL. Each 10 mL vial of DP contains an extractable volume of not less than 8. (b) (4) mL of product and excipients: (b) (4) sodium phosphate (b) (4) sodium chloride, (b) (4) mannitol, and (b) (4) Poloxamer 188. The DP is sterile, contains no preservative, and is stored at $\leq -60^{\circ}\text{C}$. Each vial is packaged into an individual secondary carton.

For shipping of frozen labeled vials in secondary cartons (Finished Goods or FG) the applicant has validated use of two different third-party shippers. Each of these shippers has been validated to hold a minimum of (b) (4) FG carton and a maximum of (b) (4) FG cartons with a validated shipping window of up to (b) (4) hours on (b) (4) (depending on which

shipper is used). After receipt at the clinical site, frozen vials are stored at $\leq -60^{\circ}\text{C}$. Vials are thawed at room temperature (RT). Once thawed DP can remain at RT (up to 25°C (77°F)) for a maximum of 10 hours, including the time for preparation and infusion. If necessary, an intact vial (stopper not yet punctured) that has been thawed at room temperature can be stored refrigerated between 2 to 8°C (36 to 46°F) for up to 3 days, upright and protected from light (e.g., in the original carton).

The manufacturer accepts raw materials based on specified quality attributes, including identity, concentration, and purity. No raw materials derived from animals or humans are used in manufacturing and non-animal derived materials are appropriately controlled to ensure the absence of microbial contaminants.

The control strategy includes testing of the (b) (4), DP, (b) (4) for (b) (4), identity, purity, strength, and potency. Most process-related impurities are removed, however (b) (4) impurities including the (b) (4)

The levels of these (b) (4) impurities are controlled by lot release specifications. (b) (4)

Testing showed that there are (b) (4)

The strength of the (b) (4) DP is measured by (b) (4)

Validation data demonstrates that the (b) (4) assay is precise, however it is not a direct measurement of (b) (4). Instead, it relies on the (b) (4)

During the original BLA submission the Applicant proposed changing the assay used to measure product concentration (strength) from the (b) (4) assay, which was used throughout development, to the (b) (4) assay. While this remained a review issue following issuance of the CR letter, additional analytical characterization data and assay control information provided in the BLA resubmission and investigated during the pre-license inspection support implementation of the (b) (4) assay for DP strength determination and dosing.

The potency of drug product lots are controlled using several assays, including (b) (4) based assays that measure (b) (4)

Stability

The FBDS is stable for (b) (4) days at (b) (4) months when stored at the long-term (b) (4) storage temperature ((b) (4)). The DP is stable for 36 months when stored at the long-term frozen storage temperature. Once thawed, DP can remain at ambient temperature (up to 25°C) for a maximum of 10 hours, including the time for preparation and infusion. If necessary, an intact vial (stopper not yet punctured) that has been thawed at room temperature can be stored refrigerated (2-8°C) for up to 3 days, upright and protected from light (e.g., in the original carton).

Comparability

Throughout clinical trials the manufacturing process was optimized and (b) (4). The current manufacturing process produces DP with a subset of critical quality attributes that are not comparable to those of the initial Phase 1/2 clinical lots. However, the current manufacturing process produces an acceptable product and was utilized for the Phase 3 clinical study.

B. RECOMMENDATION

I. APPROVAL

This biological license application (BLA) provides an adequate description of the manufacturing process and characterization of the DP valoctocogene roxaparvovec-rvox, The CMC review team has concluded that the manufacturing process, along with associated test methods and control measures, can yield a product with consistent quality characteristics. The information provided in this BLA, satisfies the CMC requirements for biological product licensure per the provisions of section 351(a) of the Public Health Service (PHS) Act controlling the manufacture and sale of biological products.

Post-Marketing Commitments (PMCs):

None (No CMC PMCs)

Approved Comparability Protocols:

None

Lot release requirements:

The approved product is subject to a Lot Release Protocol, which is provided in the DBSQC review memorandum. (b) (4) DP release testing results will be verified by CBER reviewers, prior to introduction of any lot into interstate commerce.

II. COMPLETE RESPONSE (CR)

N/A

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
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Andrew Harmon Ph.D., Lead Biologist OGT/DGT1/GTB1	Concur	Andrew Harmon -S Digitally signed by Andrew Harmon -S Date: 2023.06.21 09:15:00 -0400
Y Nguyen Ph.D., Biologist OGT/DGT1/GTB2	Concur	Y N. Nguyen -S Digitally signed by Y N. Nguyen -S Date: 2023.06.21 07:34:03 -0400
Mikhail Ovanesov, PhD, Supervisory Research Chemist OPPT/DH/HB2	Concur	Mikhail Ovanesov -S Digitally signed by Mikhail Ovanesov -S Date: 2023.06.21 08:50:01 -0400
Denise Gavin, Ph.D. Chief, Gene Therapy Branch 1 OGT/DGT1/GTB1	Concur	Denise K. Gavin -S Digitally signed by Denise K. Gavin -S Date: 2023.06.20 21:56:27 -0400
Kimberly Schultz, Ph.D. Chief, Gene Therapy Branch 4 OGT/DGT1/GTB4	Concur	Kimberly L. Schultz -S Digitally signed by Kimberly L. Schultz -S Date: 2023.06.21 07:30:27 -0400
Denise Gavin, Ph.D. Director, Office of Gene Therapy CMC	Concur	Denise K. Gavin -S Digitally signed by Denise K. Gavin -S Date: 2023.06.20 21:57:20 -0400

Review of CTD

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Module 3

3.2.S DRUG SUBSTANCE

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

(Reviewed by AH)

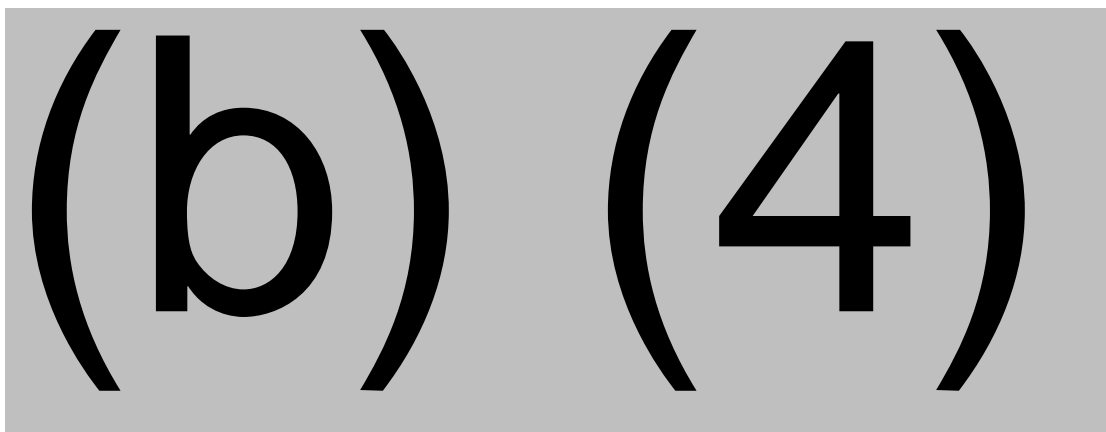
3.2.S.1.1 Nomenclature

Table 1: Nomenclature

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3.2.S.1.2 Structure

(b) (4)

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(b) (4)

3.2.S.1.3 General Properties

Reviewed in the OS CMC Review Memo

3.2.S.2 Manufacture
3.2.S.2.1 Manufacturer(s)

Drug Substance	
Facility	Responsibility

(b) (4)

44 pages have been determined to be not releasable: (b)(4)

Reviewer Comment:

(b) (4)

Overall Reviewer's Assessment of Section 3.2.S.7:

(b) (4)

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

Reviewed in the Original Submission CMC Review Memo

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

Reviewed in the Original Submission CMC Review Memo

3.2.P.2.1.2 Excipients

Reviewed in the Original Submission CMC Review Memo

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

Reviewed in the Original Submission CMC Review Memo

3.2.P.2.2.2 Overages

Reviewed in the Original Submission CMC Review Memo

3.2.P.2.2.3 Physicochemical and Biological Properties

Reviewed in the Original Submission CMC Review Memo

3.2.P.2.3 Manufacturing Process Development

Reviewed in the Original Submission CMC Review Memo

3.2.P.2.4 Container Closure System

Note that this section is for discussion of the CCS in the context of pharmaceutical development, which was reviewed in the original BLA submission CMC review memo. Additionally see [Section 3.2.P.7](#) of this review memo.

3.2.P.2.5 Microbiological Attributes

Reviewed in the Original Submission CMC Review Memo

3.2.P.2.6 Compatibility

Reviewed in the Original Submission CMC Review Memo

Overall Reviewer's Assessment of Section 3.2.P.2:
Acceptable. See original BLA submission CMC review memo.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Facility	Responsibility
BioMarin Pharmaceutical Inc. (BPI) Novato Campus (b) (4) Novato, CA, 94949 USA FEI: 3004079983	Drug Product Manufacture Drug Product Filling Drug Product Storage Primary Labeling <ul style="list-style-type: none"> (b) (4) Labeling of Vials (Primary and only site for (b) (4) labeling) Drug Product In-process Testing <ul style="list-style-type: none"> (b) (4) (b) (4) Drug Product Release Testing <ul style="list-style-type: none"> (b) (4) Appearance (b) (4) Extractable Volume (b) (4) Poloxamer 188 Content (b) (4) Endotoxin Stability Testing <ul style="list-style-type: none"> (b) (4) Appearance Container Closure Integrity (b) (4)
(b) (4)	Primary Labeling <ul style="list-style-type: none"> Frozen labeling of vials (Primary and only site for frozen labeling) Secondary Packaging

(b) (4) FEI: (b) (4)	<ul style="list-style-type: none"> Packaging of (b) (4) frozen labeled vials (Primary and only site for secondary packaging)
(b) (4) FEI: (b) (4)	Storage
(b) (4) FEI: (b) (4)	Drug Product Release Testing <ul style="list-style-type: none"> Sterility
(b) (4) FEI: (b) (4)	Drug Product Release Testing <ul style="list-style-type: none"> (b) (4) Stability Testing <ul style="list-style-type: none"> (b) (4)
(b) (4) FEI: (b) (4)	Drug Product Release Testing <ul style="list-style-type: none"> Sterility

Reviewer Note: The tabulation of manufacturers represents formalization of the following changes negotiated during the OS BLA CMC Review

(b) (4)

Acceptable.

3.2.P.3.2 Batch Formula

Reviewed in the Original Submission CMC Review Memo

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:

The information provided adequately describes the manufacturing facilities and batch formula associated with commercial DP manufacturing.

During CMC review of the original submission, the Applicant agreed to remove (b) (4) from the list of manufacturing and facilities associated with BMN270. Further, the Applicant agreed that (b) (4) would be the primary and only site for both frozen labeling operations and secondary packaging operations. These changes are reflected in the BLA resubmission.

3.2.P.3.3 Description of Manufacturing Process

Reviewed in the Original Submission CMC Review Memo

Overall Reviewer's Assessment of Section 3.2.P.3.3:

The description of the DP manufacturing process was reviewed in the original BLA submission CMC review memo and is acceptable.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Reviewed in the Original Submission CMC Review Memo

Overall Reviewer's Assessment of Section 3.2.P.3.4:

The information describing the critical steps of the DP manufacturing procedure and the mechanisms used to control these steps, were reviewed in the original BLA submission CMC review memo and are acceptable. In-process (b) (4) are adequately described and the validation of those holds was reviewed in Section 3.2.P.3.5 of the original BLA submission CMC review memo.

3.2.P.3.5 Process Validation and/or Evaluation

Manufacturing process validation and PPQ studies were reviewed in the Original Submission CMC Review Memo. This information included not only validation of the DP manufacturing process, but also validation of

- Labeling operations for applying primary vial labels to previously frozen (b) (4) vials, i.e., ability to complete manual labeling without DP temperature excursion.*
- Adherence of primary vial labels to previously frozen (b) (4) vials following labeling, storage, and shipment.*

Additionally, validation of labeling operations was also discussed in detail at the Novato Manufacturing Facility PLI, including review of appropriate control measures in place to prevent mix-ups of unlabeled (b) (4) vials (i.e., appropriate labeling and sealing of secondary containers containing (b) (4) reconciliation of (b) (4) at shipping/storage/labeling stages, dedicated storage space at the labeling facility for the ROCTAVIAN product, labeling campaigning and clearance etc.).

In their resubmission, the Applicant has included additional validation data to support:

1. the use of the DP (b) (4) and the (b) (4) associated with the (b) (4). These data include:
 - a. Additional information on the (b) (4)
 - b. Updated validation report PVR-240187
 - c. Updated validation report, PVR-240216 supporting new (b) (4)
 - d. Updates to section 3.2.P.3.5.8.1 regarding (b) (4) sanitation
 - e. (b) (4) validation and (b) (4) data.

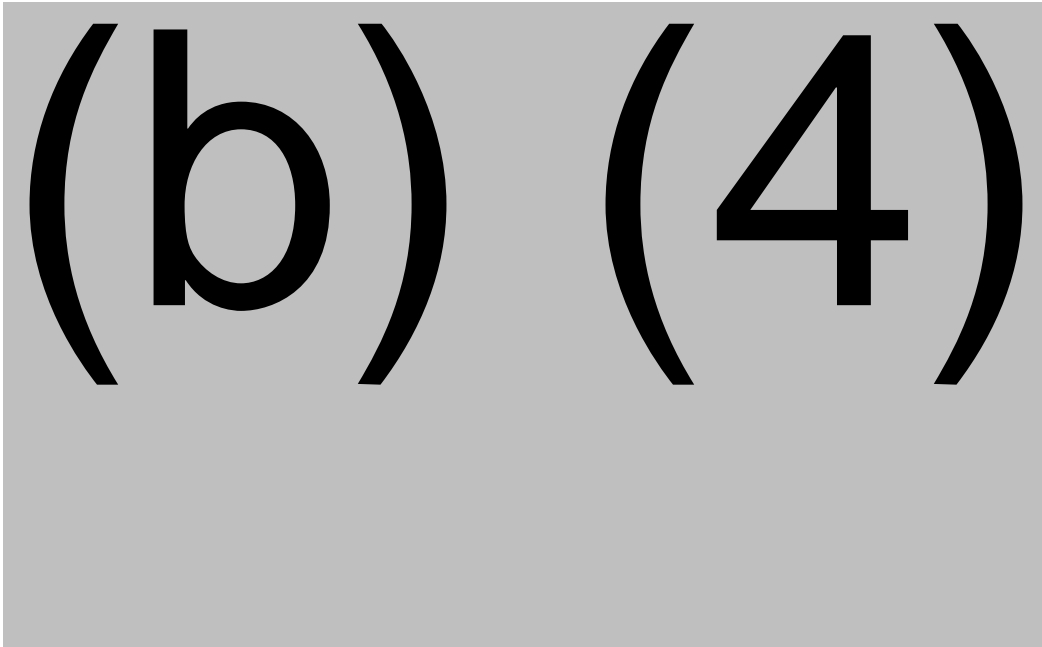
This additional information was reviewed by the DMPQ discipline and is acceptable. See DMPQ memo for details.

2. The validation of additional third party shippers (b) (4) for the following shipping lanes (b) (4)

Table 20: Qualified Shipping Configurations for DP

(b) (4)

Table 21: Shipping Configuration Validation Summary



Reviewer Notes:

1. Shipping configurations introduced in the BLA resubmission are denoted in red.
2. Validation of the new shipping configurations was reviewed by a ORA/OMPTO/OBPO/BPIS reviewer attached to the DMPQ review discipline team during the pre-license inspection and was found to be acceptable. See DMPQ memo and PLI EIR for details.

Overall Reviewer's Assessment of Section 3.2.P.3.5:

The information submitted to Module 3.2.P.3.5 demonstrates the DP manufacturing process is well controlled and capable of making a consistent DP that meets commercial specifications.

In the BLA resubmission, the Applicant submitted additional validation data to support the use of the DP (b) (4) and the (b) (4) associated with the (b) (4). As well as new validation data for additional DP shipping configurations. This data is acceptable.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

Reviewed in the Original Submission CMC Review Memo

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

Reviewed in the Original Submission CMC Review Memo

3.2.P.4.4 Justification of Specifications

Reviewed in the Original Submission CMC Review Memo

3.2.P.4.5 Excipients of Human or Animal Origin

Reviewed in the Original Submission CMC Review Memo

3.2.P.4.6 Novel Excipient

Reviewed in the Original Submission CMC Review Memo

Overall Reviewer's Assessment of Section 3.2.P.4:

The information to support the control of the excipients used in the DP (b) (4) (b) (4) was reviewed in the original BLA submission CMC review memo and is acceptable.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Table 22: Commercial DP Release Specifications

Parameter	Method	Release
AAV5 Vector Genome Identity	(b) (4)	
AAV Serotype 5 Capsid Identity	(b) (4)	
Appearance	(b) (4)	Clear, colorless to pale yellow liquid, essentially free of visible particulates
(b) (4)	(b) (4)	(b) (4)
Extractable Volume	(b) (4)	NLT 8.0 mL/vial
	(b) (4)	
(b) (4)		

(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Sterility	(b) (4)	No growth
Endotoxin	(b) (4)	(b) (4)
Poloxamer 188 Content	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Reviewer Note: The justification for a (b) (4) was reviewed by MO and is acceptable. See the OS BLA CMC Memo and the supplemental BLA Re-submission supplemental review memo on bioanalytical methods used for analysis of clinical samples for review details.

The table above represents the negotiated and acceptable commercial release specifications for the DP. See sections [3.2.S.4.1](#) and [3.2.S.4.5](#) for analysis of the justifications for specifications revised during review of the BLA resubmission and negotiations with the Applicant, as the analytical methods reviewed are shared between (b) (4) DP release.

Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:

The revised release specifications for BMN270 DP are acceptable.

See sections [3.2.S.4.1](#) and [3.2.S.4.5](#) for review of release specifications negotiated during review of the BLA resubmission as the analytical methods reviewed are shared between (b) (4) DP release.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

Most procedures were reviewed during the OS review cycle and evaluated as acceptable to support the BLA. A few tests were revised during the resubmission. See sections [3.2.S.4.3](#) and [3.2.S.4.4](#) for review of analytical methods revised in the BLA resubmission and their validation, as the analytical methods reviewed are shared between (b) (4) DP release.

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

Collectively, the information provided and reviewed in the original BLA submission CMC review memo, and additional information provided in the BLA resubmission and during the pre-license inspection, demonstrate that the analytical methods intended for commercial release of DP are appropriate and are suitable for their intended purpose.

3.2.P.5.4 Batch Analyses

(Reviewed by AH, EAG, and YN)

Batch analysis, including process changes, comparability, and demonstration of product manufacture consistency was reviewed in the Original Submission CMC Review Memo. In the resubmission, the Applicant has submitted new release testing data for (b) (4)/DP lots. This data represents testing of proposed commercial product lots. While this data further supports manufacturing consistency, the previously submitted data from process (b) (4) (shown to be safe and effective in clinical studies) is the primary data set for setting release specifications. Acceptable.

3.2.P.5.5 Characterization of Impurities

Reviewed in the Original Submission CMC Review Memo

Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:

The data in 3.2.P.5.4 as reviewed in the original BLA submission CMC review memo, and this resubmission memo, is acceptable to demonstrate that the applicant can manufacture the final drug product with consistent quality attributes. All DP batches passed pre-determined acceptance criteria for release. Noticeable statistical differences in the population mean of early stage vs late stage product potency were noted. Detailed assessment is cross-referenced to Section 3.2.S.2.6 (Comparability) of the original BLA submission CMC review memo.

Release acceptance criteria were negotiated and tightened during BLA resubmission review and updated release specifications are acceptable.

Analysis of impurities is cross-referenced to 3.2.S.3.2 of the original BLA submission CMC review memo as DP manufacture consists only of final filtration and finish/fill. Acceptable.

3.2.P.6 Reference Standards or Materials

The same reference material is used for testing (b) (4) DP. New information about the reference standard was reviewed in (b) (4) sections (see Section 3.2.S.5 Reference Standards or Materials).

3.2.P.7 Container Closure System

(Reviewed by AH)

The container closure system and shipping validation were reviewed in the Original Submission CMC Review Memo. Additionally, a summary of the consult

extractable/leachable review memo was included in Section 3.2.S.6 of the original submission CMC review memo. Regarding the BLA resubmission, the applicant has:

- 1. Formally updated this section to reflect responses to information requests during the original review cycle. This includes correction to the units in BLA Figure 3.2.P.2.4.2.1.*
- 2. Provided additional information on the compatibility of the (b) (4) vial container closure system with shipment on (b) (4)*

Compatibility of the (b) (4) vial container closure system with shipment on (b) (4)

During the PLI activities associated with the BLA resubmission, BioMarin submitted an update regarding studies in response to the (b) (4)

(b) (4) of DP shipped on (b) (4) in (b) (4) vials. During the inspection data from Technical Report TR- 242908 (b) (4)

(b) (4) showed clear findings that the principal drivers of product (b) (4) were a.) Longer exposure of DP to (b) (4) and b.) longer storage of DP at refrigerated conditions post-thaw.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Figure 23 above shows decreases in BMN270 (b) (4) as assessed each day post thaw for samples that were previously frozen (b) (4) days. Longer durations spent exposed to (b) (4) resulted in a quicker drop of (b) (4) reached the lower specification limit of (b) (4) for BMN 270 after (b) (4) days in 2-8 °C for the vials exposed to (b) (4) for (b) (4) days, 3 days for (b) (4) days in (b) (4), and (b) (4) days for (b) (4) days in (b) (4)

BioMarin concluded that (b) (4) changes drastically over the course of the (b) (4) in 2-8 °C (post-thaw) after (b) (4) exposure. Although additional studies did not show an effect of the (b) (4) drop on product CQA's, BioMarin has modified the package insert of the proposed commercial DP to limit storage of vials post thaw (at refrigerated conditions) to less than or equal to three days to control for product (b) (4) at clinical sites. Additional studies regarding feasibility of (b) (4) (b) (4) during shipping are on-going and changes may be submitted as a post-approval supplement.

Reviewer Note:

The finding that product (b) (4) is driven by length of vial exposure to (b) (4) and storage time (post-thaw) at refrigerated conditions is supported by the Applicants data. Control of the (b) (4) attribute (post-thaw) by limiting the in-use expiry is appropriate. The package insert was reviewed and the instructions regarding in-use stability were confirmed. Acceptable.

Overall Reviewer's Assessment of Section 3.2.P.7:

The data relevant to the proposed container closure system (CCS) demonstrates the proposed CCS is acceptable for use in commercial manufacture of the DP.

3.2.P.8 Stability

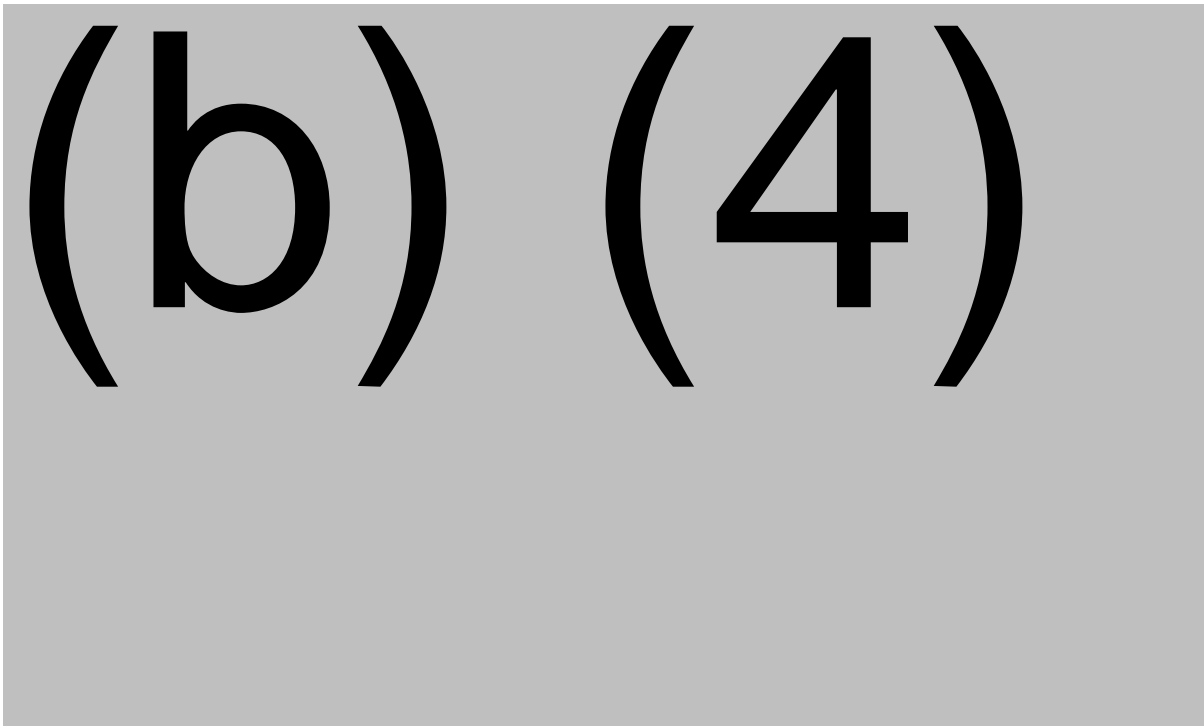
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

(Reviewed by EAG)

In the original BLA submission, the information provided to support the shelf-life of the DP was inconclusive because the DP lots used for the stability study were all generated from FBDS stored at (b) (4) but did not include FBDS stored (b) (4). Of note, the validated commercial manufacturing process allows for storage of FBDS at either of these conditions.

In the BLA resubmission, the Applicant has revised the FBDS storage conditions used to generate the DP lots used in their stability studies. The FBDS storage conditions outlined below demonstrate the various lots used in the stability study, how the FBDS lots were stored at (b) (4), and how the DP was stored following manufacture.

Figure 24: Stability Studies on DP (b) (4) FBDS Storage Conditions

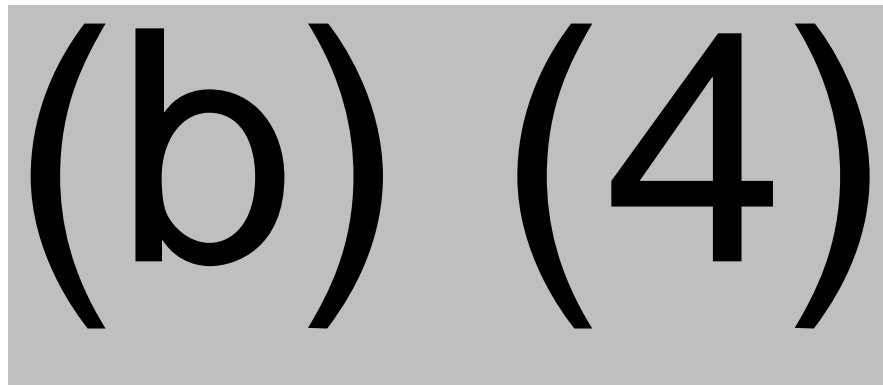


In the BLA re-submission, the Applicant proposed a shelf-life of 24-months for the final DP. Note that during the review cycle the Applicant changed their proposed expiry for DP from 24-months to 36-months (Amendment #100, submitted on 4/14/23). The data were re-reviewed in the context of this request.

Relevant data provided in the BLA resubmission to support the proposed shelf-life is summarized below.

The stability data for the DP generated from FBDS stored in both validated conditions (i.e., (b) (4)) is summarized below. The data for FBDS stability are discussed in the FBDS stability section (see 3.2.S.7.1 and 3.2.S.7.3 Stability Data). Note that only data on relative potency is shown in this memo. All other measured CQAs were unchanged within the study period.

Figure 25: Relative Potency Stability for BMN 270 DP at Intended Storage Condition

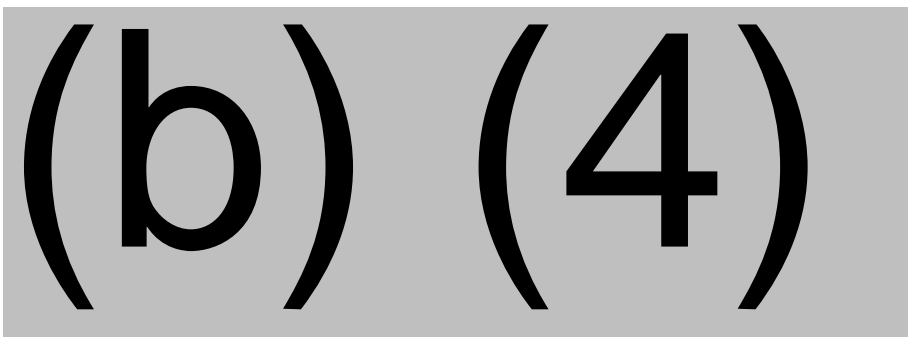


Notes on the above data:

- (b) (4)

Reviewer Note: Available real-time stability data support the proposed 36 months shelf-life for the DP stored at $\leq -60^{\circ}\text{C}$. This is acceptable.

Figure 26: Accelerated Relative Potency Stability for BMN 270 DP.



Reviewer Comment: Accelerated stability studies were also performed in accordance with (b) (4).

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

The Applicant has committed to assessing the stability of (b) (4) commercial lot of BMN 270 DP manufactured (b) (4). Lots will be placed on stability (b) (4) at (b) (4) and monitored according to the protocol. Ongoing stability studies will be monitored through (b) (4) months. FBDS Lot (b) (4) will be (b) (4) of storage at (b) (4) and processed into a DP lot. The DP lot will be placed on stability at the (b) (4) and (b) (4) stability conditions.

Table 23: BMN 270 Post-Approval DP Stability Testing Plan

A large rectangular area is completely redacted with a solid grey fill. The text "(b) (4)" is printed in large, bold, black font across the center of this redacted area.

Reviewer Note:

The specification for the potency under stability is slightly wider than the release specification even though no clear trend is seen in the potency stability data of the commercially representative CP (b) (4) DP lots. Based on reviewer calculation, the proposed stability criterion (for potency) is more stringent than a 2-sided 95CI/97 tolerance interval for (b) (4) DP lots used in the clinical trial. Therefore, the proposed stability specification is acceptable.

The post-approval stability protocol, including the test schedule, associated methods, storage conditions and acceptance criteria for BMN 270 drug product is acceptable.

Overall Reviewer's Assessment of Section 3.2.P.8:

Based on the data reviewed in the original BLA submission, and additional data submitted in the BLA resubmission, the proposed drug product shelf-life of 36 months at intended storage condition of $\leq -60^{\circ}\text{C}$ is supported by the data and is acceptable.

In the original BLA submission, the applicant had requested a 30-month shelf-life for the drug product. This was not supported by the required minimum number of representative lots. The additional data provided in the BLA re-submission (originally provided to support a 24-month expiry and subsequently a 36-month expiry are adequate to support the proposed labeling.

The testing plan for the Applicant's post approval stability protocol is acceptable.

3.2.A APPENDICES**3.2.A.1 Facilities and Equipment**

Note that a Pre-license facility inspection for the Novato manufacturing facility was conducted during BLA resubmission review. The facilities and equipment used for commercial manufacture of the BMN270 product are acceptable. See the DMPQ discipline CMC review memo and the Novato establishment inspection report (EIR) for full details.

Overall Reviewer's Assessment of Section 3.2.A.1:

The facilities and equipment used for commercial manufacture of the BMN270 product are acceptable. See the DMPQ discipline CMC review memo for full details.

Note that a Pre-license facility inspection for the Novato manufacturing facility in support of this BLA was conducted during the resubmission review period. See the establishment inspection report (EIR) for full details.

3.2.A.2 Adventitious Agents Safety Evaluation

See below for review of specific subsections of Module 3.2.A.2

Materials of Biological Origin:

Reviewed in the Original Submission CMC Review Memo

(b) (4) Studies

Reviewed in the Original Submission CMC Review Memo

Overall Reviewer's Assessment of Section 3.2.A.2:

The information provided in Module 3.2.A.2 was reviewed in the original BLA submission CMC review memo and is acceptable to demonstrate negligible risk posed by materials of biological origin and to demonstrate that robust (b) (4) is achieved by the (b) (4) steps of the manufacturing process.

3.2.A.3 Novel Excipients

There are no novel excipients used in the formulation of BMN 270.

3.2.R Regional Information (USA)

❑ Executed Batch Records

Reviewed in the Original Submission CMC Review Memo

❑ Method Validation Package

(Reviewed by EAG and YN)

The method validation reports for analytical methods performed for the release of (b) (4) DP are reviewed and discussed under sections [3.2.S.4.3](#) and [3.2.P.5.3](#) of this Memo.

❑ Combination Products

BMN270 is not a combination product.

Overall Reviewer's Assessment of Combination Products Section:

BMN270 is not a combination product.

❑ Comparability Protocols

The BLA resubmission does not contain a comparability protocol or post-approval change management protocols.

3.2.R.2 Analytical Standard Operating Procedures

Reviewed in the Original Submission CMC Review Memo

Lot Release Protocol

(Reviewed by AH, EAG, and YN)

BMN270 (b) (4) DP are subject to CBER lot release (lot release protocol (LRP) review, without in-support testing) and the LRP template review was conducted by the DBSQC discipline in consult with the DGT1 CMC reviewers. See the DBSQC review memo for full details.

Reviewer Note: *The revised release specifications negotiated and agreed in to review memo section above have been incorporated into the LRP and this document is acceptable for documentation of released (b) (4) DP.*

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

The applicant's environmental assessment is provided in 1.12.14, in accordance with 21 CFR 25. This application is not eligible for categorical exclusion, and the applicant does not make a claim of categorical exclusion. The applicant does not propose any alternative action other than approval.

The product valoctocogene roxaparvovec-rvox is derived from AAV5, a non-pathogenic human DNA virus that is incapable of autonomous replication. AAV5 genes have been replaced with a DNA genome that does not express any viral proteins. The product is capable of a single round of transduction (delivery of DNA to a cell), but there is no possibility of additional replication or infection. The manufacturing process is designed to minimize the potential that DNA recombination might result in a virus that contains DNA for viral genes, and each product lot is tested for the absence of replication-competent AAV (rcAAV). Even if rcAAV were to form, the virus would still be non-pathogenic and incapable of replicating and causing infectious disease.

The product is manufactured using insect cells and recombinant baculovirus and therefore carries a theoretical risk of being contaminated with adventitious agents (viruses or bacteria). Although baculovirus may be present, the manufacturing process efficiently inactivates and removes the baculoviruses and chances of baculovirus being present in the final product are very low. The production of potentially immunogenic baculovirus proteins from the vector DNA fragments is highly unlikely. The insect cells are tested to ensure absence of adventitious agents, and each lot of product also undergoes in-process testing to ensure absence of adventitious agents. The manufacturing process is also validated to remove or inactivate model viruses.

This product will be administered at hospitals or treatment centers using universal precautions, and unused product and product-contact materials will be disposed of as biohazardous medical waste. The product is relatively stable (compared to other viruses) at room temperature, but will degrade over time into naturally-occurring materials.

Data from a clinical study demonstrate that patients who are treated with valoctocogene roxaparvovec-rvox shed vector DNA in saliva, urine, semen, and stool with peak concentrations observed between 1 and 9 days post-administration, and then concentrations steadily declined to undetectable or low residual levels over the duration of follow-up. Patients may shed vector DNA in stool for up to 88 weeks, but shorter periods of time after administration for saliva (69 weeks) and urine (8 weeks). DNA will also be

shed in semen for extended periods of time after administration; however, encapsidated vector DNA was cleared from semen by 12 weeks.

For vector DNA detected in saliva, urine, and stools, it is not known how much of the shed DNA is encapsidated in AAV capsids, as opposed to shedding of naked DNA. Even if encapsidated, the risk of causing infectious disease is low because the product is inherently incapable of causing infectious disease. Toxic effects from exposure to small amounts of this vector or vector encoded transgene would be unlikely, even if it is intact.

The likelihood of germline transmission of vector DNA through semen is negligible. Animal studies showed no indication of paternal germline transmission to the offspring. Please refer to pharmacology/toxicology review memo for additional details. The AAV vector DNA in the semen is present in the seminal fluid and not in the sperm cells, which is necessary for the germline transmission to the host progeny genome.

Reviewer's comment: It can be concluded that there will be no significant environmental impact from approval of valoctocogene roxaparvovec-rvox, and a finding of no significant impact (FONSI) will be prepared.

Viral DNA Clearance (Shedding)

(Reviewed by YN)

The vector shedding analyses were assessed in Studies 270-207 (N=7) and 270-301 (N=134). In both studies, levels of vector DNA were monitored using validated qPCR assay. The vector infectivity was not tested; however, the shedding of potential infectious vector DNA was evaluated by measuring the concentrations of encapsidated vector DNA by immunoprecipitation coupled quantitative PCR (iqPCR). A subject was considered to no longer be shedding vector DNA if they had a negative (below limit of detection) laboratory result of 3 or more consecutive time points. Due to the high sensitivity of the qPCR method and for clearance of clinically meaningful quantities of vector DNA, BioMarin defines a negative result as the time to below the lower limit of quantification (BLQ) of the qPCR method. The summarized clearance data below represents the time to the first BLQ confirmed by 2 additional consecutive measurements.

In both studies, following 6E13vg/kg administration, vector DNA was detected in saliva, semen, urine, and stool with peak concentrations detected between 1 and 9 days post-administration in all subjects. The highest median peak concentrations were observed in saliva followed by semen, stool, and urine. The maximum concentration in any shedding matrix was 1E10 vg/mL. Following peak concentrations, vector DNA levels gradually declined to undetectable or low residual levels.

All subjects (N=141) cleared the vector DNA in urine and saliva with the maximum clearance time of 8 and 69 weeks, respectively. By the data cut-off time, 120 (85%) and 139 (98%) of the subjects no longer shed the vector DNA in their stools and semen, respectively. The maximum clearance time was 88 (stools) and 36 (semen) weeks. Encapsidated vector DNA was cleared from the semen by 12 weeks. Two subjects had

detectable vector DNA in semen more than 52 weeks after administration. Isolated sperm cells from these two subjects were tested and vector DNA was not detected, suggesting the vector DNA detected in semen was not associated with germline cells. Likewise, paternal germline transmission was not observed in two nonclinical studies conducted in mice with BMN270. Therefore, the likelihood of germline transmission is negligible.

Encapsidated vector DNA was assessed only in semen. The qPCR assay used to monitor shedding for the other matrices only measure vector DNA. Therefore, it is not known how much of the shed DNA is encapsidated in AAV capsids, as opposed to shedding of naked DNA. Even if encapsidated, the risk of causing infectious disease is negligible because the product is inherently incapable of causing infectious disease, and there will be no direct toxic effects from exposure to small amounts of this vector, even if it is intact.

B. Reference Product Designation Request

The applicant has requested reference product designation in section 1.3.5.3 of the original BLA submission CTD.

The Reference Product Exclusivity Determination Board (meeting held on April 27, 2023) agreed to designate valoctocogene roxaparvovec-rvox as a reference product.

C. Labeling Review

(Reviewed by AH)

Full Prescribing Information (PI):

The following sections were reviewed.

Sections 2 (Dose and Administration) and 3 (Dosage Forms and Strengths)

The DP is supplied frozen ($\leq -60^{\circ}\text{C}$) at a nominal concentration of 2×10^{13} vector genomes (vg)/mL in individually cartoned vials containing an extractable volume of 8mL. The recommended dose of the product is 6×10^{13} vg per kilogram (vg/kg) of body weight administered as an intravenous infusion.

Dose preparation involves first calculating the dose in mLs based on the patient's body weight (using a pre-specific dose calculation formula) followed by calculation of the number of vials of ROCTAVIAN required to be thawed (using a pre-specified calculation formula). DP is extracted from thawed vials into infusion-pump syringes. The thawed product (in vials or syringes) is stable for a maximum of 10 hours (supported by in-use stability studies, see section 3.2.P.8 of this memo). If necessary, an intact vial (stopper not yet punctured) that has been thawed at room temperature can be stored refrigerated between 2 to 8°C (36 to 46°F) for up to 3 days, upright and protected from light (e.g., in the original carton). The product is administered through an in-line filter ($0.22\mu\text{m}$).

***Reviewer Note:** During labeling negotiations the Applicant made several changes to clarify in-use stability times and to add details regarding how the product is prepared.*

Section 11 (Description)

ROCTAVIAN (valoctocogene roxaparvovec-rvox) is an adeno-associated virus (AAV) vector-based gene therapy product. ROCTAVIAN is replication-incompetent and consists of an AAV serotype 5 capsid containing a DNA sequence encoding the B-domain deleted SQ form of the human coagulation factor VIII (hFVIII-SQ). ROCTAVIAN is derived from naturally occurring adeno-associated virus and is produced using Sf9 insect cells and recombinant baculovirus technology.

ROCTAVIAN is a sterile suspension for intravenous infusion. When thawed, the suspension is clear and colorless to pale yellow.

Reviewer Note: The original package insert (PI) refers to ROCTAVIAN as a solution. In an IR (sent on 2/27/23) the applicant was asked to revise this description to "suspension". In Amendment #98 (received 3/6/23) the Applicant agreed to this change.

Section 12 (Clinical Pharmacology)

Valoctocogene roxaparvovec-rvox is an adeno-associated virus serotype 5 (AAV5) based gene therapy vector, designed to introduce a functional copy of a transgene encoding the B-domain deleted SQ form of human coagulation factor VIII (hFVIII-SQ). Transcription of this transgene occurs within the liver, using a liver-specific promoter, which results in the expression of hFVIII-SQ. The expressed hFVIII-SQ replaces the missing coagulation factor VIII needed for effective hemostasis.

Shedding studies are described in section 12.3 of the PI, based on review of shedding data from 140 evaluable subjects from Studies 270-201 and 270-301 ([See Module 1](#) Section of this review memo above). Section 12.3 also contains a description of the biodistribution of the vector (evaluated in nonclinical studies).

Section 16 (How supplied / storage and handling)

The product is supplied in individually cartoned vials. The number of cartons shipped to clinical centers depends on the weight of the patient. Vials are not kitted, and a single NDC number is used for each individually packaged vial/carton. The product is shipped frozen (b) (4). Upon receipt, cartons are stored frozen ($\leq -60^{\circ}\text{C}$) until ready to dose preparation.

Reviewer Note: The information provided in the PI is consistent with information in the BLA. The PI contains adequate instructions for dose preparations and administration. With appropriate instructions regarding the in-use stability of thawed vials.

Carton and Container Label:

(Reviewed by AH)

The vial and carton labels submitted in the BLA re-submission contained several errors. The Applicant was asked by an IR (Sent on 2/27/23) to make corrections and clarifications. The Applicant satisfactorily addressed labeling issues in Amendment #98 (received on 3/6/23). Please refer to the regulatory project manager (RPM)'s review memo for additional details.

Figure 27: Drug Product Vial Sample Label

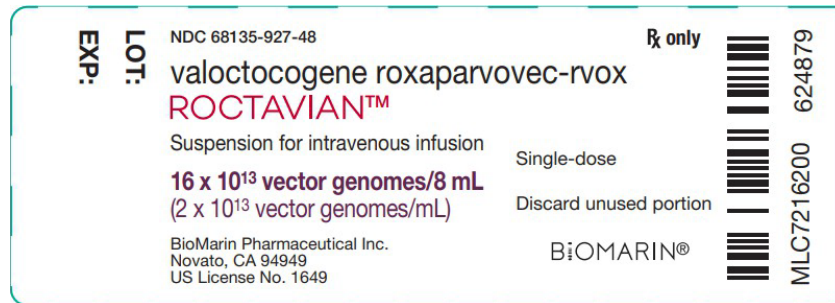
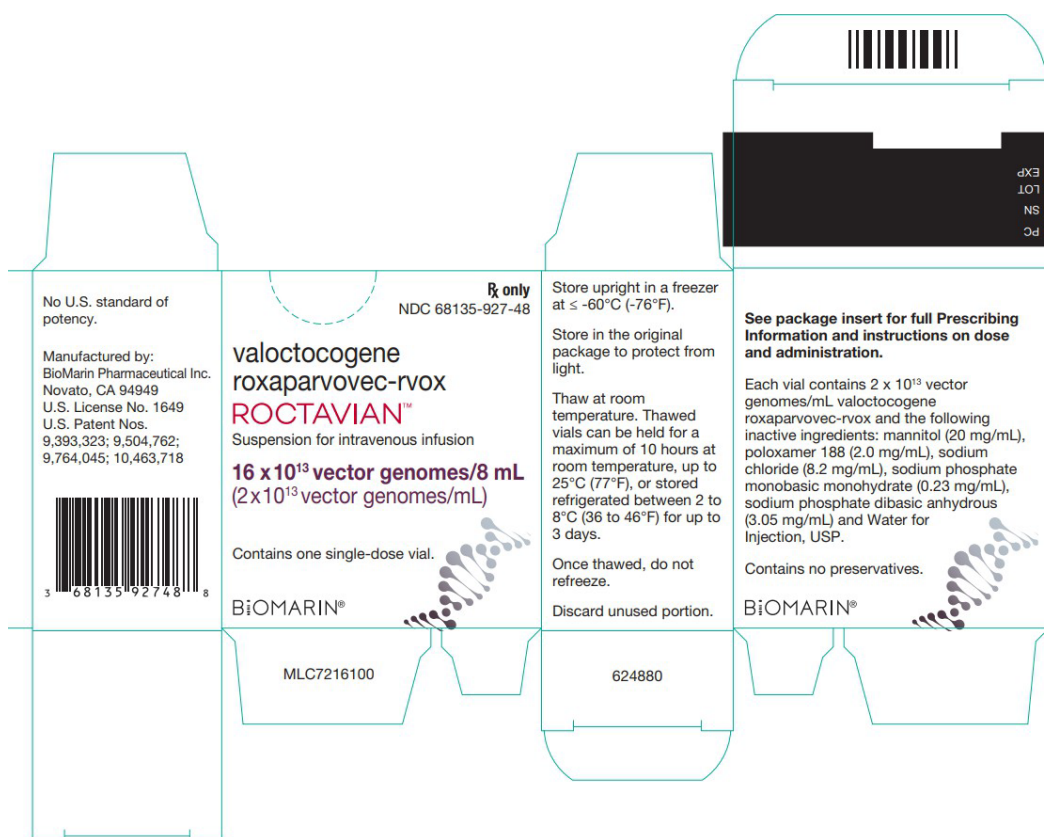


Figure 28: Carton Sample Label



Modules 4 and 5

Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

Reviewed in the Original Submission CMC Review Memo

Overall Reviewer's Assessment of Relevant Sections of Module 4 and 5:

The bioanalytical assays used to assess pharmacodynamics of BMN 270 by FVIII activity by chromogenic substrate (CS) and one-stage clotting (OC) assays and FVIII antigen by (b) (4) in patient samples were properly validated and demonstrated acceptable variability for factor activity assays in a clinical laboratory. The average ratio of OC to CS activities observed in BMN 270 patients was 1.5 as reported by BioMarin's central contract laboratory. The average ratio values reported by local laboratories are expected to range from 1.3 to 2.0 depending on the OC reagents and CS kits in use. This information will be communicated in the label.

Other assays used in clinical studies, but not manufacture have been validated and review of these assays is documented in the original BLA submission CMC review memo.